DISSERTATION

on

A STUDY OF CORRELATION BETWEEN LEVELS OF ACUTE PHASE REACTANTS (SERUM CRP, SERUM FIBRINOGEN) AND SEVERITY OF ALBUMINURIA IN PATIENTS WITH TYPE II DIABETES MELLITUS

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CERTIFICATE

This is to certify that the dissertation titled **"A STUDY OF CORRELATION BETWEEN LEVELS OF ACUTE PHASE REACTANTS (SERUM CRP, SERUM FIBRINOGEN) AND SEVERITY OF ALBUMINURIA IN PATIENTS WITH TYPE II DIABETES MELLITUS"** is a bonafide work done **by Dr.R.S.UMAAMAHESHWARI**, Post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai -03, in partial fulfillment of the University Rules and Regulations for the award of Degree of MD General Medicine (Branch – I), Internal Medicine, under our guidance and supervision, during the academic year 2014 – 2017.

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DECLARATION

I solemnly declare that the dissertation titled **"A STUDY OF CORRELATION BETWEEN LEVELS OF ACUTE PHASE REACTANTS (SERUM CRP, SERUM FIBRINOGEN) AND SEVERITY OF ALBUMINURIA IN PATIENTS WITH TYPE II DIABETES MELLITUS"** is done by me at Madras Medical College , Chennai – 600 003 during the period April 2016 to September 2016 under the guidance and supervision of **Prof**. **Dr. G. SUNDARAMURTHY** submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfillment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE (BRANCH-I) .

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CONTENTS

ABBREVIATIONS

ADA	AMERICAN DIABETES ASSOCIATION
ACR	ALBUMIN CREATININE RATIO
AGE	ACUTE GASTRO ENTERITIS
BMI	BODY MASS INDEX
CHOL	CHOLESTEROL
CAD	CORONARY ARTERY DISEASE
CRP	C-REACTIVE PROTEIN
CXR	CHEST X RAY
DCCT	DIABETES CONTROL AND COMPLICATION TRIAL
DKA	DIABETIC KETO ACIDOSIS
DN	DIABETIC NEPHROPATHY
DR	DIABETIC RETINOPATHY
FBS	FASTING BLOOD SUGAR
HHS	HYPERGLYCEMICHYPEROSMOLAR SYNDROME
IL	INTERLEUKINS
LDL	LOW DENSITY LIPOPROTEIN
LFT	LIVER FUNCTION TEST
OHA	ORAL HYPOGLYCEMIC AGENTS
PCR	PROTEIN CREATININE RATIO
PPBS	POSTPRANDIAL BLOOD SUGAR
RFT.	RENAL FUNCTION TEST

T2DM	TYPE 2DIABETES MELLITUS
TGL	TRIGLYCERIDE
TNF A	TUMOUR NECROSIS FACTOR ALPHA
UKPDS	UNITED KINGDOM PROSPECTIVE DIABETES STUDY
WHR	WAIST HIP RATIO

INTRODUCTION

INTRODUCTION

Diabetes is a major non communicable disease worldwide. Recent data indicate that around 390 million people across the globe have diabetes and this number is expected to rise up to 595 million over the next twenty years. In India there are about 65 million diabetics.

Diabetes is associated with both micro vascular complications (retinopathy, neuropathy, nephropathy) as well as macro vascular complications like cerebro vascular diseases, peripheral arterial diseases and cardio vascular diseases. The risk of chronic complications increase with the duration of diabetes. Several theories have been proposed for the pathogenesis of such chronic complications including –

1) Advanced glycosylation end products
2) Sorbitol pathway
3) Protein Kinase C pathway
4) Hexosamine pathway
5) Oxidative stress

Recent studies have shown that the above mentioned advanced glycation end products elicit a chronic low grade inflammation which correlates with the degree of organ damage.

Hence our study is aimed at assessing the levels of two of the markers of inflammation (acute phase reactants) namely serum CRP and serum fibrinogen in patients with long standing type 2 diabetes and determining whether they correlate with the degree of albuminuria (an indicator of the degree of nephropathy).

About 100 patients with type 2 diabetes mellitus are subjected to clinical assessment including body mass index, waist hip ratio, blood pressure as well as laboratory testing for fasting plasma glucose, serum CRP, serum fibrinogen , 24 hours urinary albumin , serum creatinine . The levels of the above mentioned acute phase reactants are compared with the levels of albuminuria and assessed for the presence of any significant correlation

AIMS AND OBJECTIVES

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PRIMARY OBJECTIVES

To study the corelation between levels of acute phase reactants (serum CRP, serum fibrinogen) and severity of albuminuria in patients admitted with type 2 diabetes mellitus.

SECONDARY OBJECTIVES

To assess the clinical and laboratory profile (BMI, WHR, BP, RFT, Fasting glucose) of diabetic patients with varying levels of Albuminuria.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Diabetes is a chronic metabolic disorder which may be defined as the presence of hyperglycaemia due to defective secretion of insulin, defective action of insulin or a combination of both. The chronically elevated glucose levels may result in long term microvascular complications like neuropathy, nephropathy and retinopathy as well as macro vascular complications like cardio vascular, cerebrovascular and peripheral vascular diseases. Pre diabetes refers to states of impaired glucose tolerance, impaired fasting glucose or HBA_1 C levels of 5.7 to 6.4.

DIABETES – HISTORICAL ASPECTS

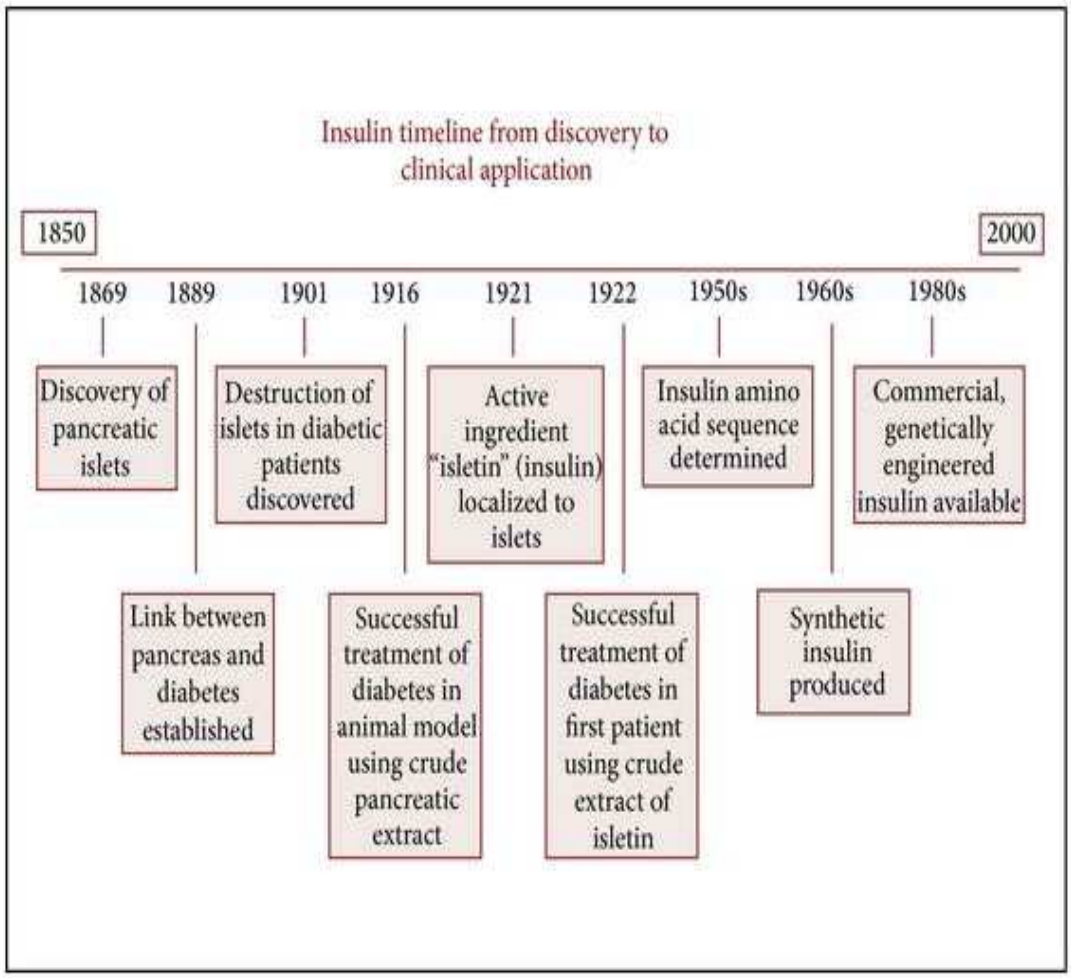
An ancient Egyptian manuscript namely the Ebers Papyrus, written in 1500 BC mentions a disease characterised by “too great emptying of the urine ”, probably referring to diabetes. Ancient Indian physicians also recognised that ants are attracted to the urine of these patients and hence termed this condition “madhumeha” or “honey urine”. In 230 BC, Apollonius of Memphis referred to this disease as *Diabetes* which means “to pass through”. The term *mellitus* which refers to honey was added later on to distinguish this disease from another disease characterised by polyuria namely diabetes insipidus.

In the fifth century AD, Indian physicians Sushrutha and Charakha had described thin individuals who developed diabetes at an earlier age and obese individuals who developed a milder form of the condition at a later age group, thus making them probably the first ever to distinguish between the two types of diabetes. In the tenth century AD, Avicenna also known as Ibn Sina described the complications of this disease including digital gangrene and sexual dysfunction.

In the year 1776, Mathew Dobson, an English physiologist proved that the urine of the diabetic patients had elevated levels of sugar. A quantitative test for detecting glucose in the urine was developed by Von Fehling in the year 1848. Frederick Banting and his student Charles Best purified and extracted insulin in the year 1921 for which the Nobel Prize was awarded. Hans Christian discovered that the addition of hagedorn can prolong the life of insulin.

With improvement of the purification and extraction techniques, longer acting insulins namely the protamine zinc insulin, neutral protamine hagedorn insulin and the lente insulins were produced. Frederick Sanger discovered the amino acid sequence of insulin which facilitated the subsequent artificial synthesis of insulin

The following chart depicts the timeline of insulin discovery. Paul Langerhans first discovered that there are specialised cells within the pancreas with endocrine function and these subsequently came to be called the islets of Langerhans.



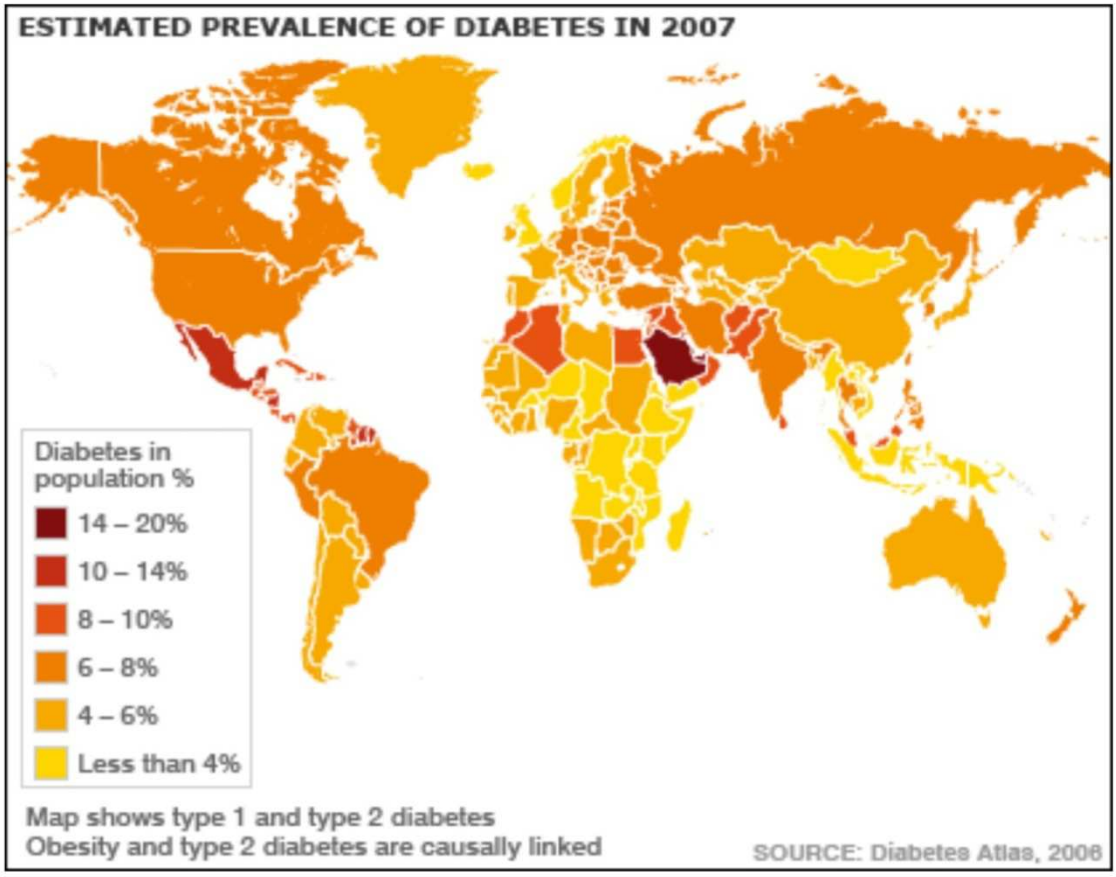
In the year 1918, C.K.Watanabe, while investigating the properties of guan iodine noted that it produced hypoglycaemia in rabbits. Hence derivatives of guanidine namely monoguanides and biguanides were developed as hypoglycaemic agents. Phenformin, a biguanides was the first effective oral hypoglycaemic agent. In the nineteen forties, Celestino

Ruiz, L.L.Silva of Argentina and M.J.Janbon of France independently observed that certain sulphonamide derivatives (which were then used as antibiotics) had hypoglycaemic properties. Subsequently potent sulfonyl urea drugs have been developed to control the sugar levels in diabetic patients.

DIABETES PREVALENCE

As per the World Health Organisation (WHO), there has been an increase in the number of people living with diabetes from 108 million in 1980 to 422 million in 2014. The overall prevalence of diabetes in people above 18 years of age has increased from 4.7 % in 1980 to 8.5 % in 2014. The developing countries have been showing a significant increase in the incidence of diabetes, probably due to their changing lifestyle patterns which subsequently lead to an increase in the proportion of overweight population. According to the data recorded in 2012, almost 1.5 million deaths globally were directly attributable to diabetes.

WORLD MAP SHOWING THE PERCENTAGE OF TYPE 2 DIABETICS AMONG THE GENERAL POPULATION



When this map was compared to the map depicting the obesity distribution across the global population , both were found to correlate with one another , indicating that obesity and type 2 diabetes are causally linked.

ECONOMIC IMPACT OF DIABETES MELLITUS

Diabetes produces a huge economic strain on the healthcare establishment of a country. The proportion of healthcare funds allotted to diabetes at the global level constituted about 11.6 %. But this expenditure on the diabetic population is not evenly distributed across age, gender and country.

Such a large economic burden due to diabetes, especially in a country like India is borne by the individual and not the state. Due to the poorly organized system of medical care, inadequate insurance coverage and uneven distribution of medical services, the people with diabetes often have to spend almost a quarter of their total income on the management of their health. Diabetic complications can result in disability, loss of life and reduced quality of life.

Several analyses have been performed in the western countries to assess the economic impact of diabetes. These have shown that there is direct and indirect cost incurred by the diabetic population.

The direct costs are as follows:

1. Physician service cost
2. Hospital service cost
3. Costs related to medications
4. Laboratory services costs

The indirect costs are as follows :

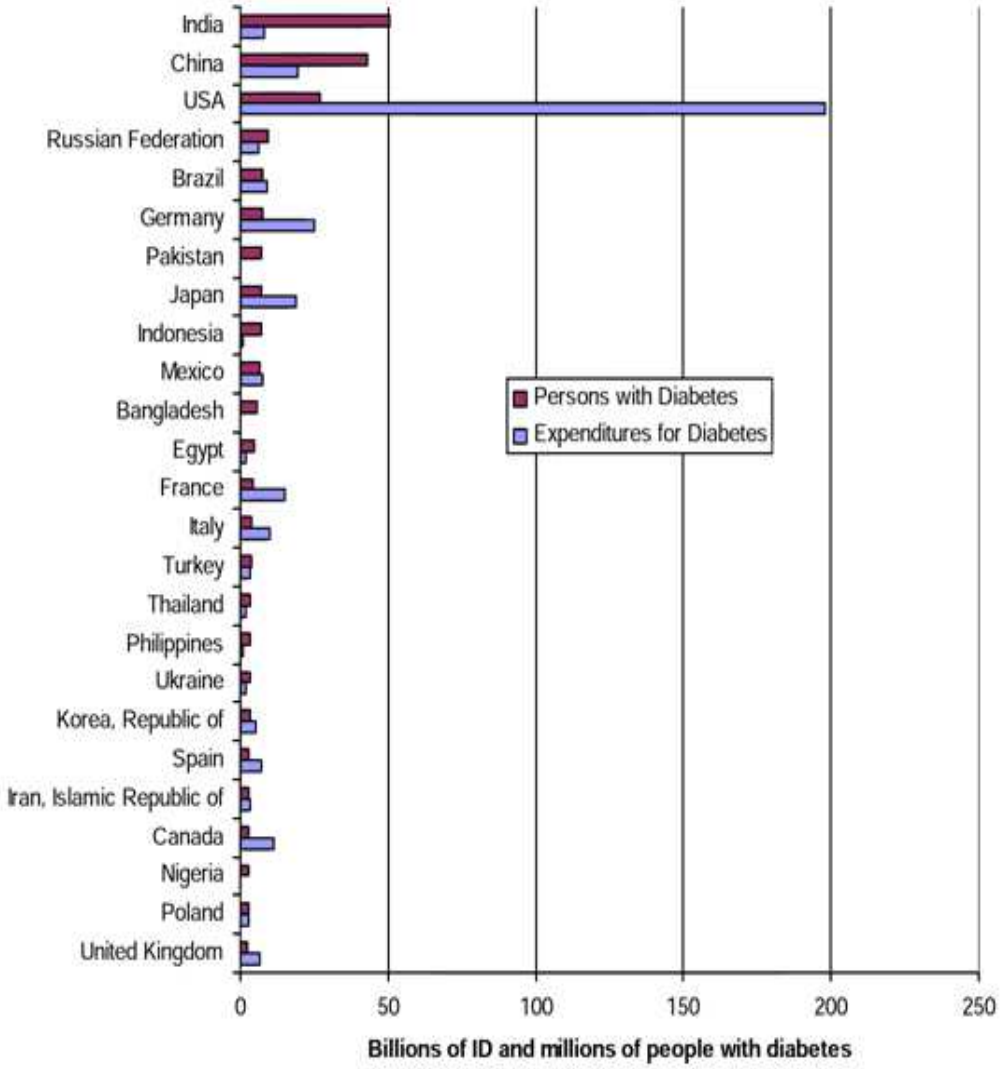
1. Loss of productivity
2. Short term morbidity
3. Permanent disability
4. Premature mortality

Diabetes is growing at an alarming pace in India. Statistics indicate that about 65.1 million people live with diabetes (compared to 50.9 million in 2010).

By 2030, probably India will have about 100 million diabetics. This striking increase in the incidence of diabetes is perhaps related to the rapid urbanization and westernisation of lifestyle. Deaths due to diabetes is also quite high (about 4 million per year).

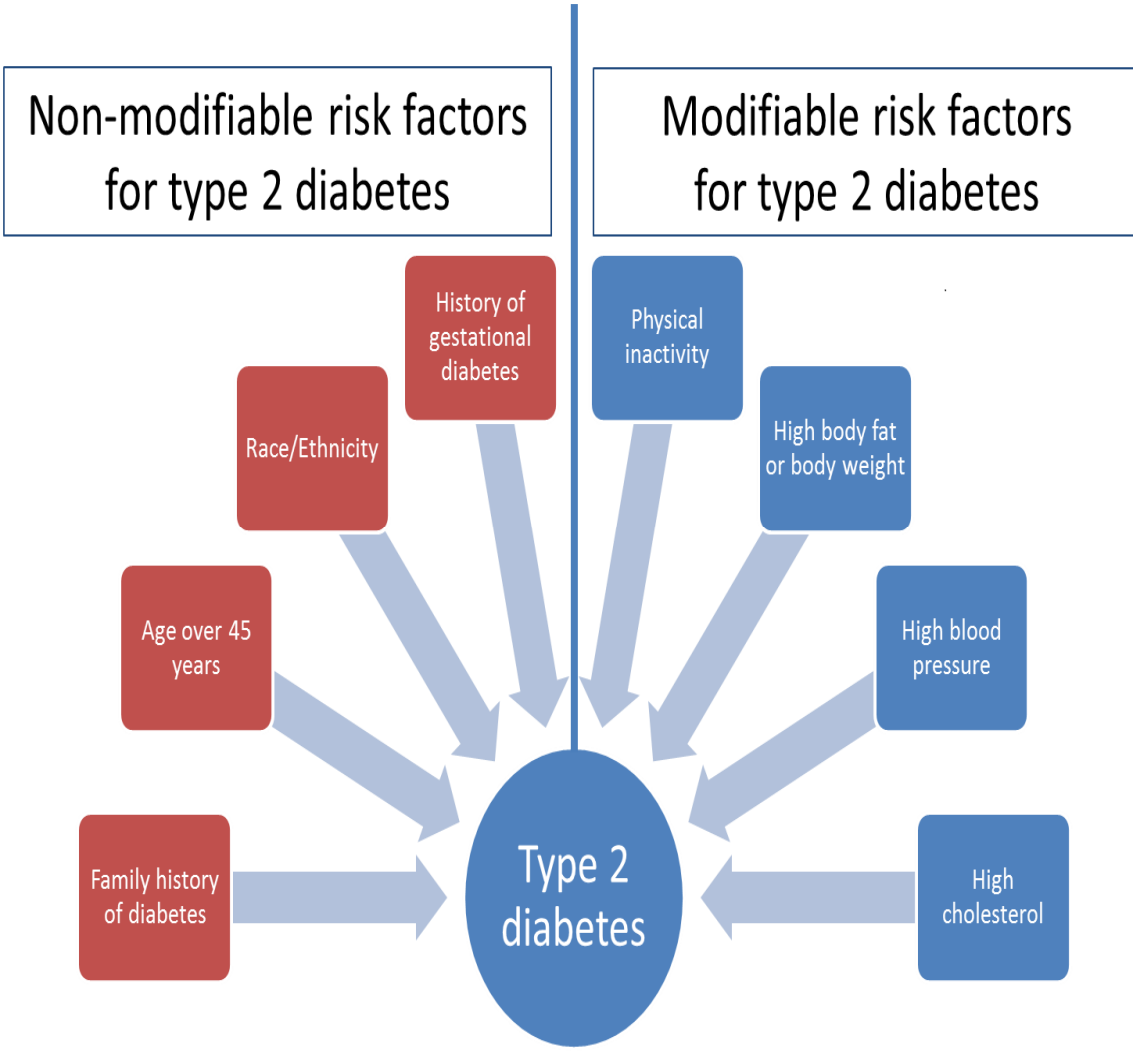
Therefore, in a developing country like India which has a very large diabetic population, early diabetes detection and prompt initiation of treatment in the outpatient setting is a must.

The following picture shows that India has one of largest diabetic populations in the world and yet it spends a disproportionate amount of funds for the their healthcare.



RISK FACTORS FOR DIABETES

The risk factors for type 2 diabetes may be classified as modifiable and non modifiable factors.



The risk factors for type 1 diabetes include genetic factors (positive family history), pancreatic diseases, infections and auto immunity.

CLASSIFICATION OF DIABETES

The World Health Organisation in collaboration with the expert committee of the American Diabetes Association formulated a widely acceptable classification of the types of diabetes. The previous terminologies namely insulin dependent diabetes and non insulin dependent diabetes were noted to be confusing and misleading and hence discarded.

As per this classification the major types of diabetes are type 1 diabetes, type 2 diabetes, gestational diabetes mellitus and other specific types. The distinction between type 1 and type 2 diabetes gains significance due to the fact that the management principles are different for both of them. These two types may be differentiated on the basis of clinical signs of insulin resistance, markers of autoimmunity (anti glutamic acid decarboxylase antibody and anti islet cell antibody) and C peptide levels. The type 1 diabetes also includes the category - LADA (latent autoimmune diabetes in adults) which refers to the patients with apparent type 2 diabetes who are however noted to have autoimmune destruction of beta cells of pancreas.

A comprehensive etiology based classification of diabetes is shown in the following table.

ETIOLOGICAL CLASSIFICATION OF DIABETES

1. Diabetes mellitus type 1
   A. Autoimmune
   B. Idiopathic
2. Diabetes mellitus type 2
   1. Insulin resistance predominates over the relative defects in hormone secretion
   2. Defects in insulin secretion predominate over the presence of insulin resistance
3. Other specific types of diabetes mellitus
   A. Genetic defects in β-cell function
      1. Chromosome 12, HNF-1α (MODY 3)
      2. Chromosome 7, glycosidase (MODY 2)
      3. Chromosome 20, HNF-4α (MODY 1)
      4. Mitochondrial DNA
      5. Others
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipotrophic diabetes
      5. Others
   C. Disease of the exocrine pancreas
      1. Pancreatitis
      2. Pancreatectomy/trauma
      3. Neoplasia
      4. Cystic fibrosis
      5. Hemochromatosis
      6. Fibrocalcific pancreatopathy
      7. Others
   D. Endocrinopathies
      1. Acromegaly
      2. Cushing syndrome
      3. Glucagonoma
      4. Pheochromocytoma
      5. Hyperthyroidism
      6. Somatostatinoma
      7. Aldosteronoma
   E. Pharmacologically or chemically induced
      1. Vacor
      2. Pentamidine
      3. Nicotinic acid
      4. Glucocorticoids
      5. Thyroid hormones
      6. Diazoxide
      7. β-adrenergic agonists
      8. Tiazides
      9. Dilantin
      10. α interferon
      11. Others
   F. Infections
      1. Congenital rubeola
      2. Cytomegalovirus
      3. Others
   G. Infrequent forms of autoimmune diabetes
      1. Stiff-man syndrome)
      2. Antibodies against insulin receptors
      3. Others
   H. Other syndromes occasionally associated with diabetes
      1. Down syndrome
      2. Klinefelter syndrome
      3. Turner syndrome
      4. Wolfram syndrome
      5. Friedreich ataxia
      6. Huntington's chorea
      7. Lawrence-Moon-Biedel syndrome
      8. Myotonic dystrophy
      9. Porphyria
      10. Prader-Willi syndrome
      11. Others
4. Gestational diabetes mellitus

GESTATIONAL DIABETES

Pregnancy can cause several changes in the maternal carbohydrate metabolic pathways. The placental hormones have an anti insulin effect and pregnancy as such is a state of insulin resistance. There has to be a

compensatory increase in the secretion of insulin to counter these effects. When this compensation is inadequate, gestational diabetes develops.

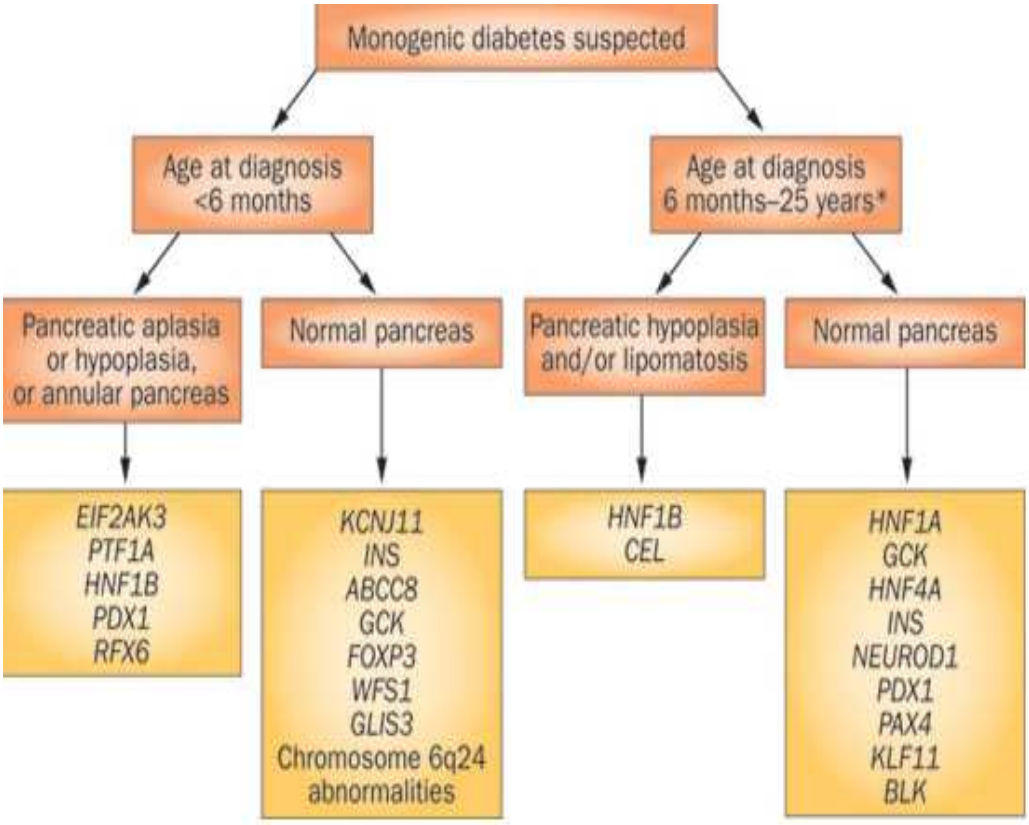
Gestational diabetes is diagnosed based on the ADA (75 or 100 gm OGTT) or (75 gm OGTT) criteria.

	ADA	ADA	WHO
	75g oral glucose (Mg/dL)	100g oral glucose (Mg/dL)	75g oral glucose (Mg/dL)
Fasting	95	95	>/= 126
1 hour	180	180	
2 hour	155	155	
3 hour	NA	140	>/= 140

OTHER TYPES OF DIABETES

(A) MONOGENIC DIABETES

Monogenic diabetes refers to a disease state characterized by single gene mutations. It usually constitutes about 1% of the diabetic population. The genetic mutations may be autosomal dominant or recessive. The monogenic diabetes categorisation is important because of the fact that it may mimic type 1 or type 2 diabetes.



A small portion of suspected type 2 diabetic population have later been found to have a late onset form of autoimmune mediated diabetes while some others have been found to have MODY and mitochondrial diabetes.

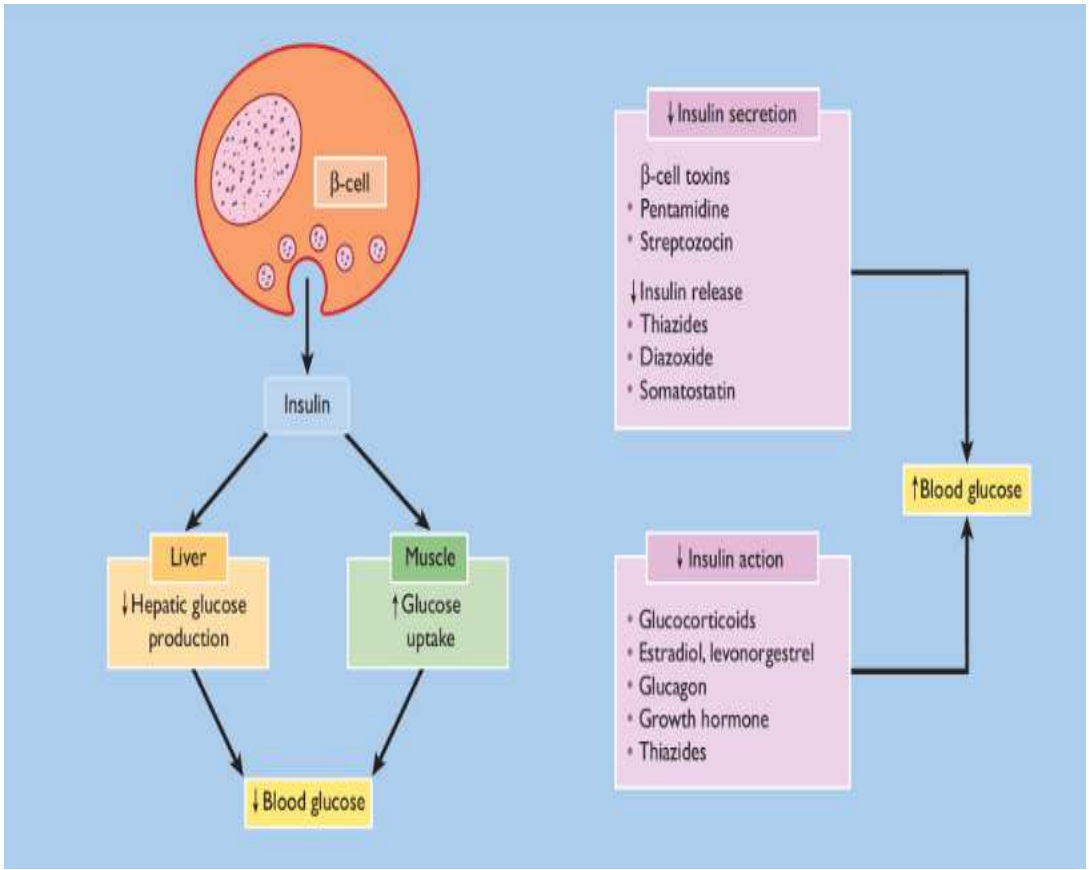
(B) DISEASES OF EXOCRINE PANCREAS CAUSING DIABETES

1. Pancreatectomy
2. Acute pancreatitis
3. Chronic pancreatitis
4. Hemochromatosis
5. Carcinoma
6. Cystic fibrosis

(C) DRUG INDUCED DIABETES

There are several drugs which can interfere with the glucose homeostasis and thereby result in a state of hyperglycemia. The most important of these are glucocorticoids, oral contraceptive pills, hormone replacement therapy, thiazide diuretics, non selective beta blockers, streptozotocin, pentamidine, cyclosporine, diazoxide, tacrolimus etc.

The list of drugs causing diabetes and the mechanisms for the same are explained in the following picture.



(D) DISEASES OF ENDOCRINE PANCREAS CAUSING DIABETES

1. Glucagonoma
2. Somatostatinoma
3. Gastrinoma
4. VIPoma
5. Carcinoid syndrome

(D) ENDOCRINOPATHIES CAUSING DIABETES

1. Acromegaly
2. Cushings syndrome
3. Pheochromocytoma
4. Hyperthyroidism
5. Hyperparathyroidism
6. Hyper aldosteronism

GLUCOSE HOMEOSTASIS

Adequate blood glucose level is essential, because the brain and RBCs utilise glucose for their function.

Maintenance of blood glucose level is under the control of several mechanisms. The body maintains glucose level with the help of two major hormones

1.INSULIN

2.GLUCAGON

INSULIN

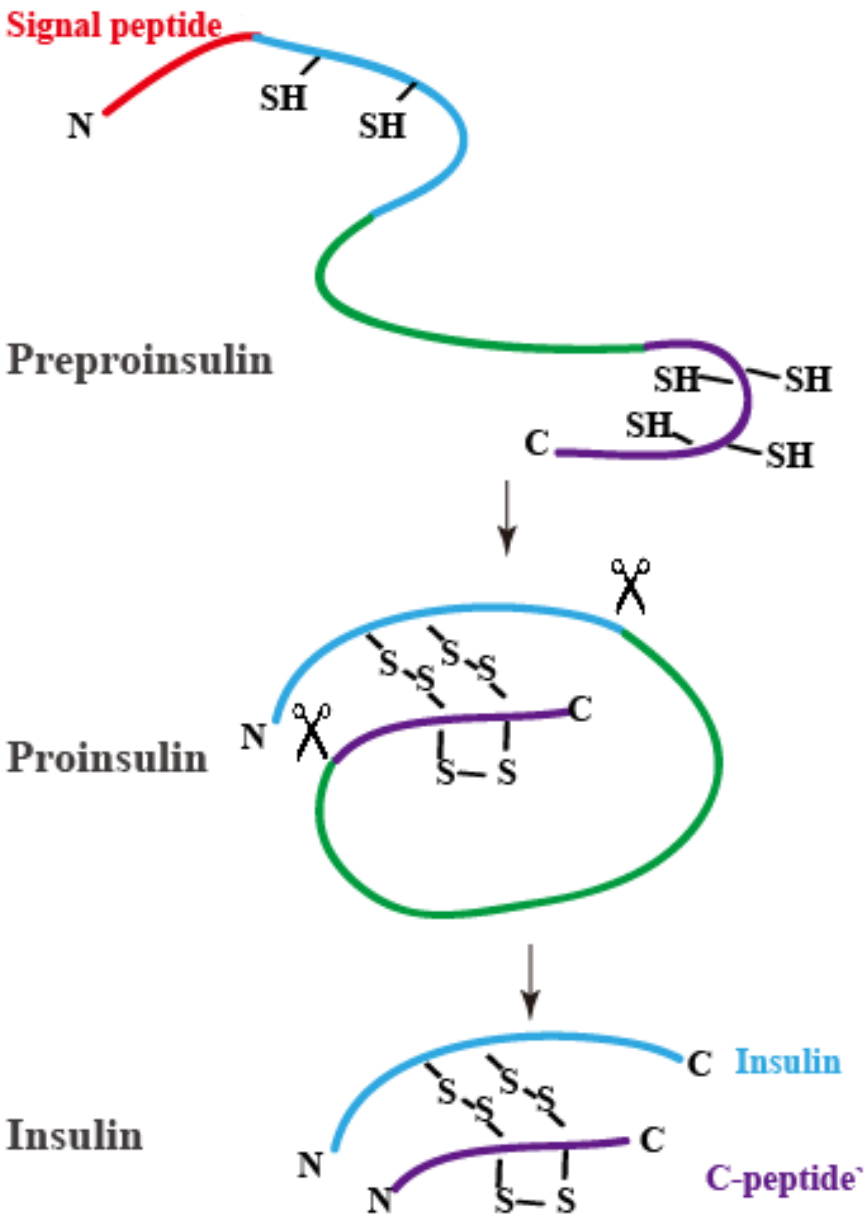
Insulin is a hormone that is produced in the islets of langerhans in the pancreas. These islets contain alpha cells, beta cells, delta cells and PP cells. The beta cells are the source of insulin, while the alpha cells secrete glucagon. Delta cells and the PP cells synthesise somatostatin & pancreatic polypeptide respectively.

INSULIN SYNTHESIS

Each of the islets of Langerhans contain about 2000 beta cells. The beta cells are particularly concentrated near the tail end of the pancreas. The human insulin gene is present in the 11p13 region of the chromosome. Initial polypeptide synthesized by the beta cell is known as the preproinsulin. This is broken down to form the pro insulin. The proinsulin is packed into vesicles which are transported in the form of granules to the surface. The pro insulin consists of insulin chain and C peptide. Therefore insulin and C peptide are released in equimolar concentrations. The beta cells have a readily available pool of pre formed insulin that can be immediately released in response to an elevation in the blood glucose levels.

The islets are stimulated by the parasympathetic to secrete insulin. The beta cells can detect even minute changes in the blood glucose levels and respond by secreting insulin. The insulin thus secreted goes and binds to the insulin receptor which is a glycoprotein composed of alpha and beta subunits. After the binding of insulin to its receptor , tyrosine kinase enzyme is activated producing a cascade reaction , finally terminating in the transcription of selective proteins.

The following picture shows the insulin synthesis from the single peptide.



INSULIN SECRETION

Insulin is secreted in response to a parenteral glucose load in a biphasic manner.

First phase :

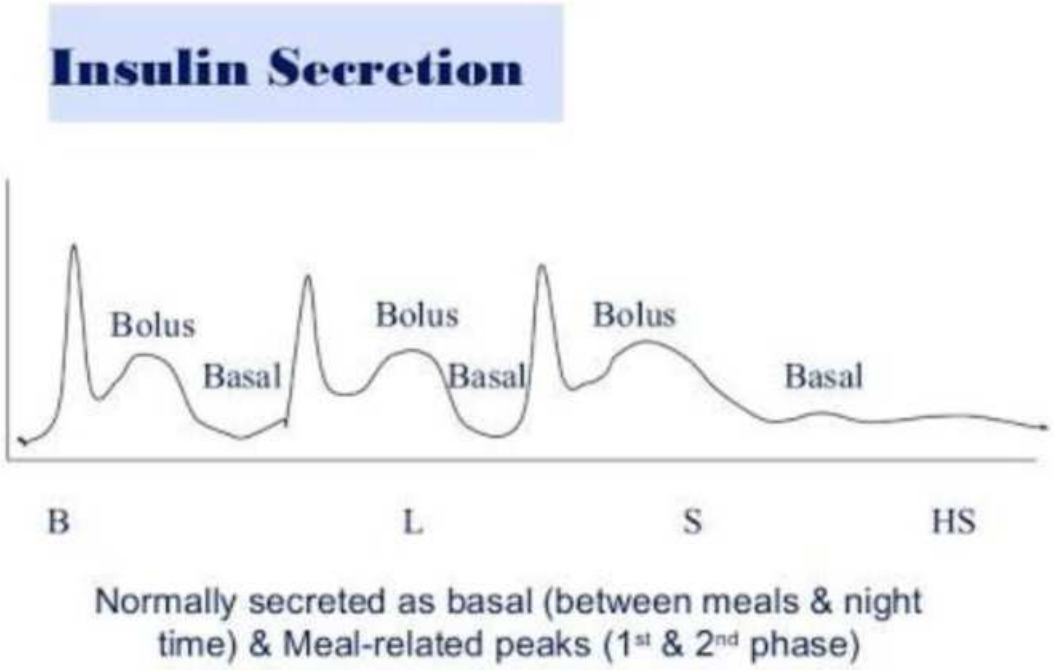
There is an initial surge in insulin levels following a glucose load which is known as the first phase of insulin secretion. This occurs approximately 2 to 3 minutes after the elevation of glucose levels. This returns to baseline within 7 to 10 minutes. The first phase is release of insulin is related to insulin secretory granules, which is located near to the beta cell membrane

Second phase:

Second phase is characterised by a slow rise in the levels of insulin. This phase insulin release is related to production of new insulin. In between these peaks, there is a basal level of insulin secretion by the islet cells. The severity of diabetes is inversely proportional to the peak of this second phase of insulin secretion.

Insulin is secreted in a continuous basal pattern as well as post prandial pulses.

The following picture indicates the secretory pattern of insulin.



The first phase and second phase release of insulin are altered in diabetics. The maximal secretary capacity of the beta cells is found to to be reduced. The amplitude of the secretory pulses is also reduced. The proportion of preproinsulin to insulin is noted to be high.

Insulin secretion throughout the day is approximately about 40 units. Secretion of insulin was found to be pulsatile.

This pulsatile secretion comprises of two pulses :-

short (rapid) pulse and

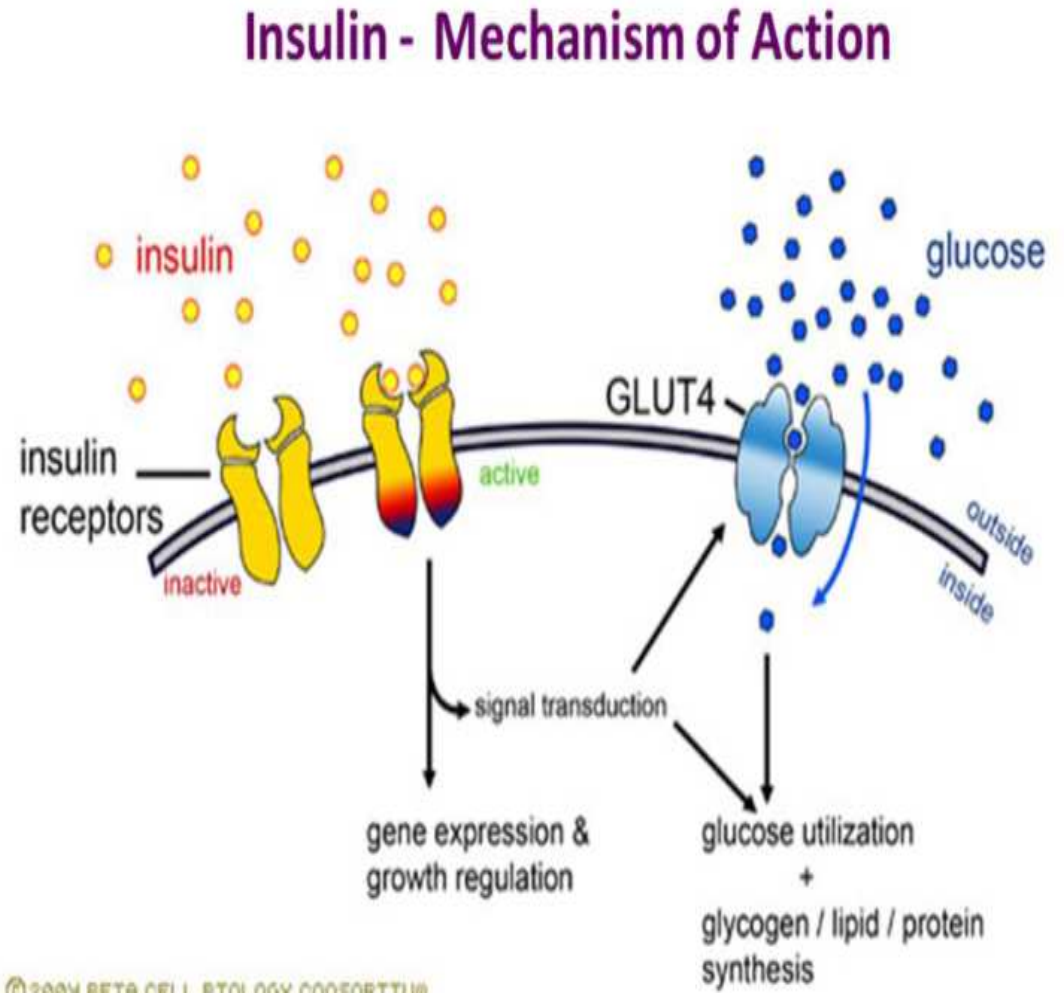
long (ultradian) pulse

This ultradian pulsation is amplified in post prandial state. These pulses are responsible for the oscillatory activity of beta cells. This oscillatory activity is an important marker for early beta cell dysfunction in type 2 diabetes mellitus.

MECHANISM OF ACTION OF INSULIN

Glucose transport across plasma membrane is mainly mediated by glucose transport proteins (GLUT). Now 13 members of the GLUT family have been identified. Among these, GLUT- 1 and GLUT- 4 are the two main isoforms mediating glucose transport in cells .

GLUT-1 is seen on the cell surface and it facilitates glucose diffusion across plasma membrane into cytosol. GLUT-4 mediates insulin stimulated glucose transport into the tissues like muscles (skeletal, cardiac) and adipose tissue.



In muscle insulin increases glucose entry, glycogen synthesis, increased amino acid uptake and protein synthesis. In liver it increases lipid synthesis and decreases glucose output. This hepatic glucose output is mainly responsible for the raised blood glucose level in a fasting state. The peripheral utilisation of glucose is determines the post prandial plasma glucose levels. Insulin acts as an anabolic as well as a catabolic hormone. In liver and kidney, insulin is metabolised by the enzyme insulinase.

PATHOGENESIS OF DIABETES

Earlier, type 2 diabetes was considered to be a disease of elderly individuals. But in recent times it has been noted to occur in adolescents and young children as well. Type 2 diabetes mellitus is caused by environmental as well as genetic factors.

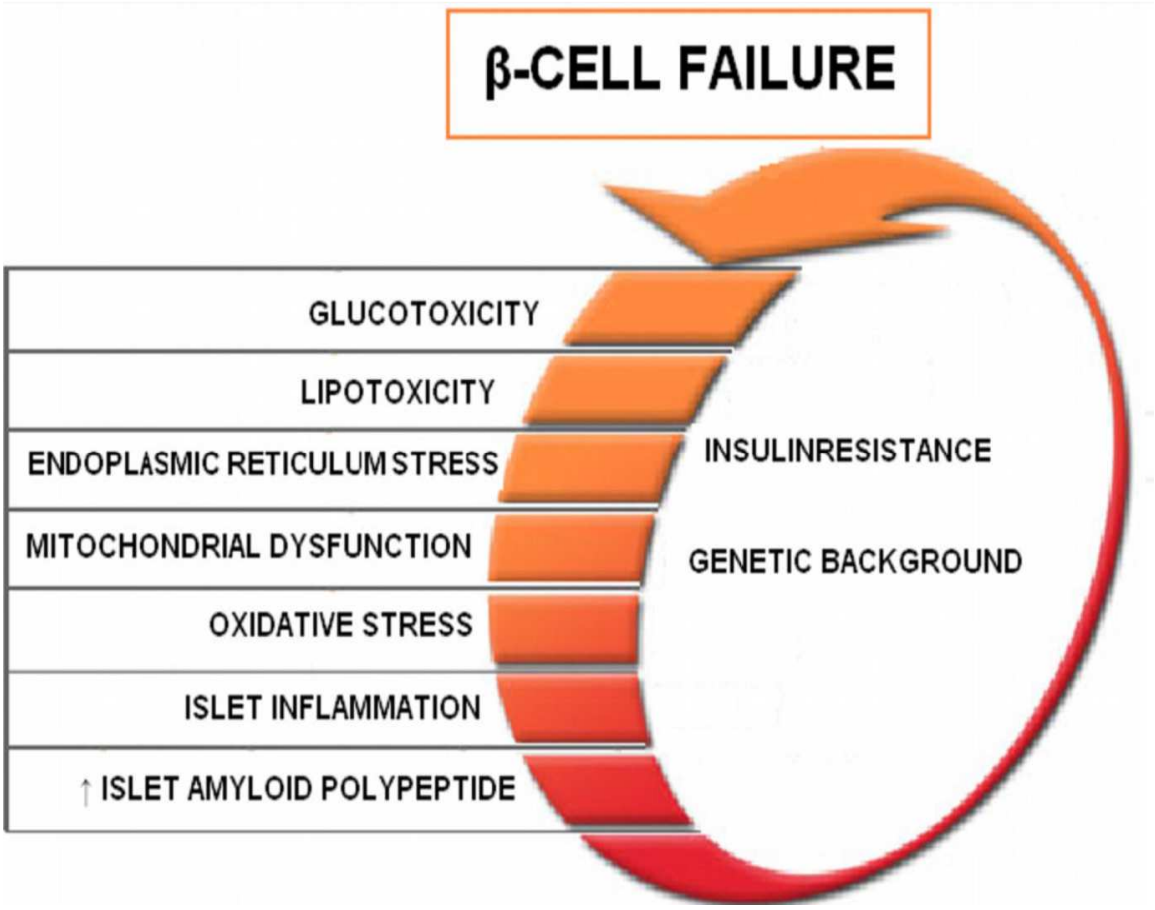
The genetic factors contribute to reduced functioning of beta cell while the environmental factors (namely sedentary lifestyle, obesity, elevated carbohydrate intake and lipid toxicity) contribute to the resistance to the action of insulin. At the time of diagnosis of type 2 diabetes itself, the beta cell function is likely to be only about 50 percentage of the normal

The theories postulated for the pathogenesis of type 2 diabetes mellitus are as follows :

1. Beta cell dysfunction (impaired insulin secretion)
2. Insulin resistance
3. Increase hepatic glucose output
4. Abnormal fat metabolism

BETA CELL DYSFUNCTION

Beta cells are situated in the islets of Langerhans in the pancreas. Main role of the beta cells is the synthesis of insulin. In type 2 diabetes mellitus, there is failure or alteration in the beta cell function. The contributory factors are glucotoxicity, lipotoxicity, ER stress, mitochondrial dysfunction, oxidative stress, islet inflammation etc.



There are several abnormalities of insulin secretion noted in type 2 diabetes mellitus. They are enlisted below

1. Reduced glucose sensing
2. Altered response of islet cells to the fluctuations of blood glucose levels
3. Inadequate first phase insulin secretion
4. Poor early insulin secretion in response to oral glucose challenge
5. Abnormalities in the rapid oscillatory phases of insulin secretion
6. Diminished effect of gastrointestinal hormones in facilitating glucose mediated insulin production (incretin effect)
7. Insufficient secretion of insulin -- such that the insulin levels do not correspond to the severity of hyperglycemia

INSULIN RESISTANCE

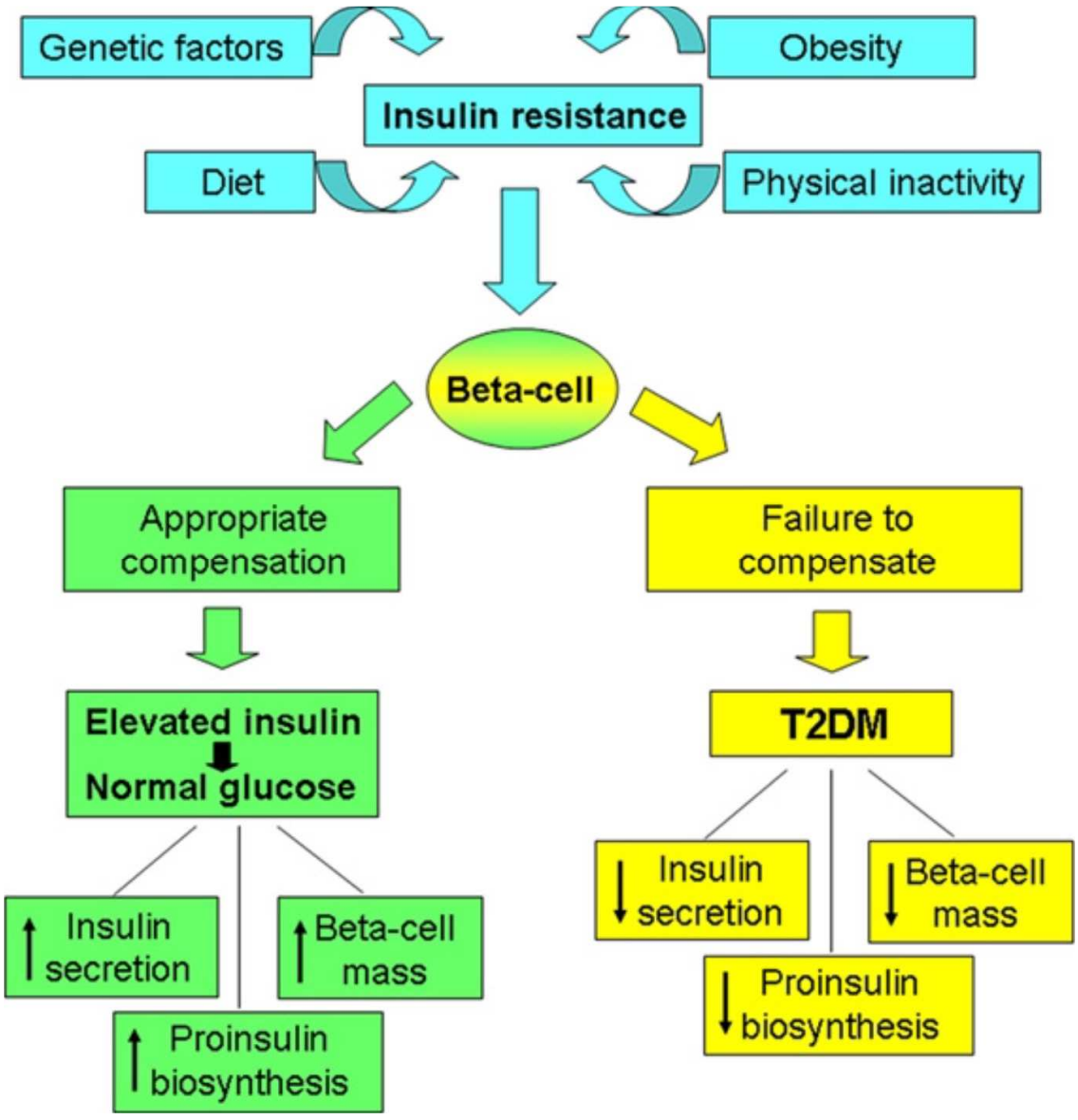
Insulin resistance refers to a state of sub optimal functional response to a specified concentration of insulin. There are various methods to quantitatively determine the insulin resistance. In type 2 diabetes, there is resistance to the action of insulin and also an absolute insulin deficiency. Often the metabolic syndrome precedes type 2 diabetes. Metabolic syndrome is characterized by the presence of insulin resistance, elevated blood pressure, altered lipid levels and visceral obesity. The criteria for the diagnosis of the metabolic syndrome is as follows

Definitions of MBS for women, according to WHO, NCEP ATP III and IDF criteria

WHO	NCEP ATP III	IDF
T2D or IFG or IGT or insulin resistance plus ≥ 2 of the following: • BMI > 30 kg/m² or WHR > 0.85 • HDL < 1.0 mmol/L (< 40 mg/dL) • TG ≥ 1.7 mmol/L (150 mg/dL) • BP ≥ 140/90 mmHg or use of blood pressure medication • microalbuminuria > 20 pg/min • Alb/Crea ratio ≥ 30 mg/g	≥ 3 of the following: • WC ≥ 88 cm • HDL < 1.3 mmol/L (< 50 mg/dL) • TG ≥ 1.7 mmol/L (150 mg/dL) • BP ≥ 135/85 mmHg or use of blood pressure medication	Central obesity defined as WC above the ethnicity-specific cut-off plus ≥ 2 of the following: • TG ≥ 1.7 mmol/L (150 mg/dL) or specific treatment • HDL < 1.3 mmol/L (< 50 mg/dL) or specific treatment • BP ≥ 135/85 mmHg or use of blood pressure medication • fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL) or previously diagnosed T2D

BP = blood pressure; HDL = high density lipoprotein cholesterol; IGT = impaired glucose tolerance; T2D = type 2 diabetes; TG = triglycerides; WC = waist circumference; WHR = waist to hip ratio.

For a certain period, the pancreatic islet cells compensate for the resistance to insulin action by increasing the quantity of insulin secreted but after a certain time interval there is a gradual decline in the functioning of the islet cells. This is followed by progressive hyperglycemia.



In these insulin resistance states, there is a reduced ability of insulin to inhibit the glucose production in the liver, thereby resulting in hyperglycemia. In the adipose tissue there is altered production of adiponectin (which normally facilitates insulin action) and reduced ability of insulin to inhibit lipolysis, as a result of which the fatty acid levels are elevated. Adiponectin deficiency is also considered to be contributory to the development of fatty liver in diabetic patients.

The insulin resistance in the hepatic tissue causes elevated levels of very low density lipoprotein and triglycerides but there is a decrease in the levels of high-density lipoprotein because cholesterol esters are removed from it by the CETP protein.

In the skeletal muscles the insulin mediated uptake of glucose is diminished glycogen synthesis is also reduced.

The following picture depicts the effects of insulin deficiency and insulin resistance on the liver, adipose tissue and the skeletal muscles.

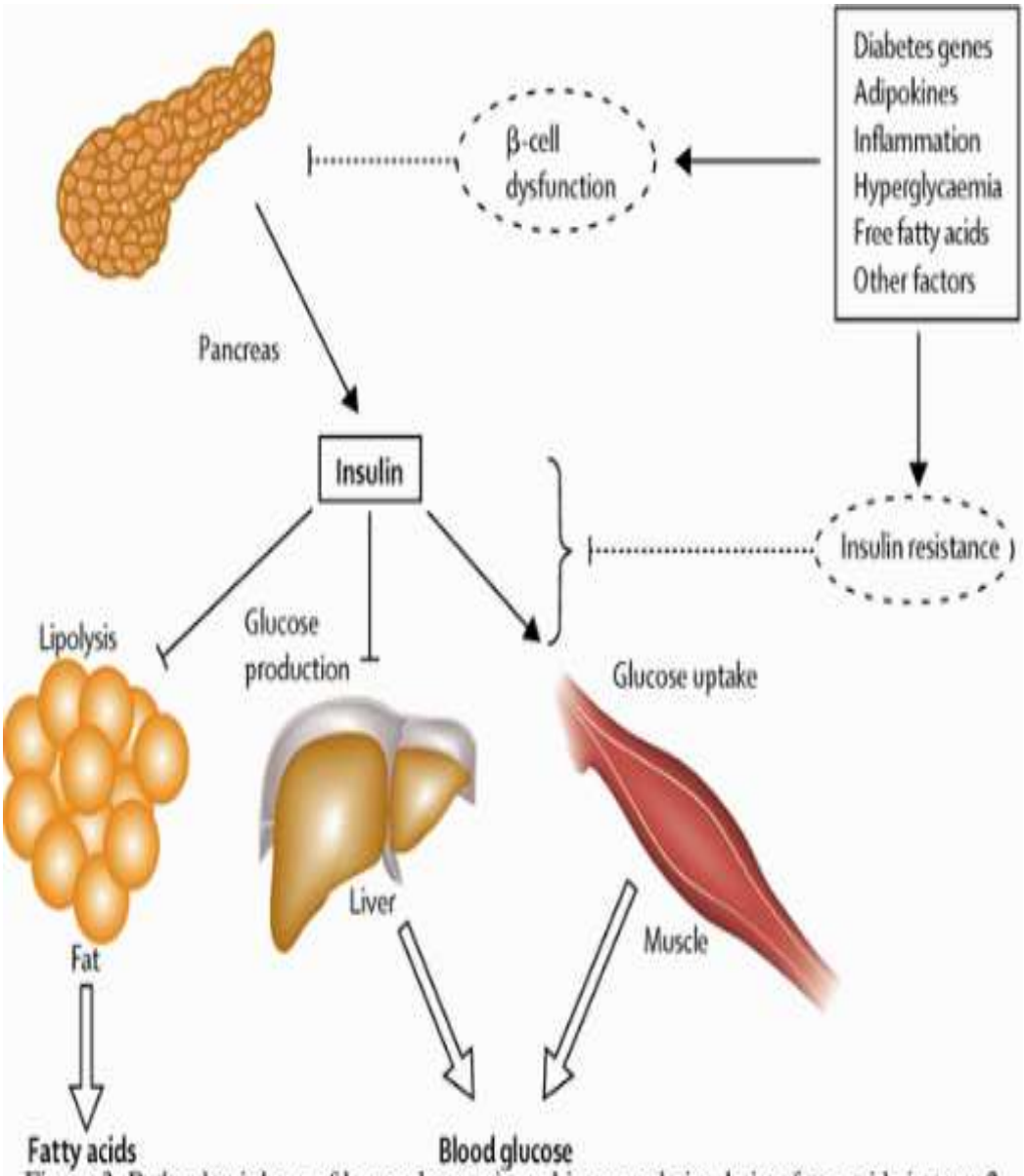


Figure 3: Pathophysiology of hyperglycaemia and increased circulating fatty acids in type 2 diabetes

COMPLICATIONS OF DIABETES

The complications of diabetes are categorised as acute and chronic complications.

1. ACUTE COMPLICATIONS

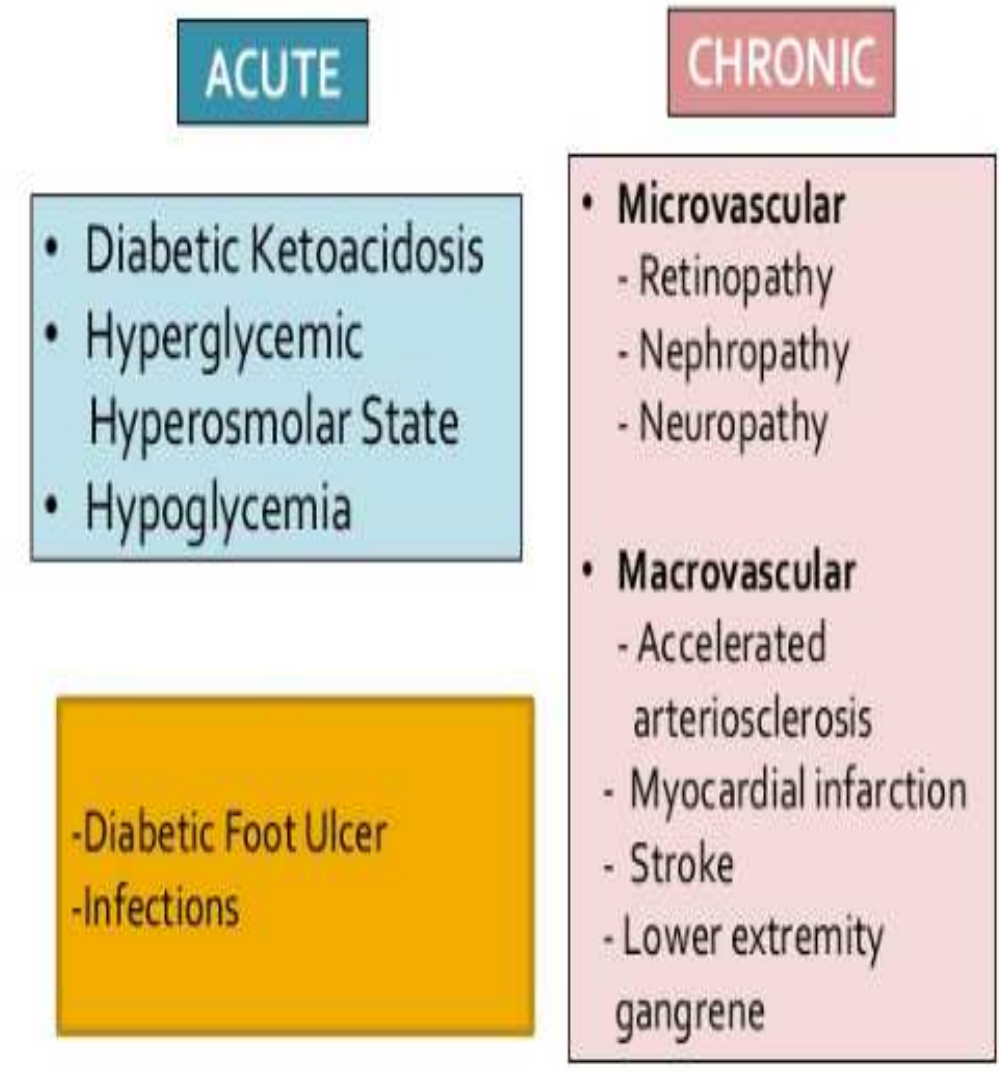
1. Diabetic keto acidosis
2. Hyper osmolar hyperglycemic state
3. Hypoglycemia (treatment related)

2. CHRONIC COMPLICATIONS

The major complications of diabetes may be categorized as micro vascular and macro vascular complications.

1. The micro vascular complications include diabetic retinopathy, diabetic nephropathy and peripheral neuropathy.
2. The macro vascular complications are cardio vascular diseases , cerebro vascular diseases and peripheral vascular diseases.

COMPLICATIONS OF DIABETES MELLITUS



ACUTE COMPLICATION:

These acute diabetic complications are considered to be medical emergencies. They are Diabetic Keto Acidosis (DKA), Hyper osmolar Hyperglycemic Syndrome (HHS) and Hypoglycemia.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis occurs due to a state of insulin deficiency and excess counter regulatory hormones. The deficiency of insulin leads to poor peripheral uptake of glucose.

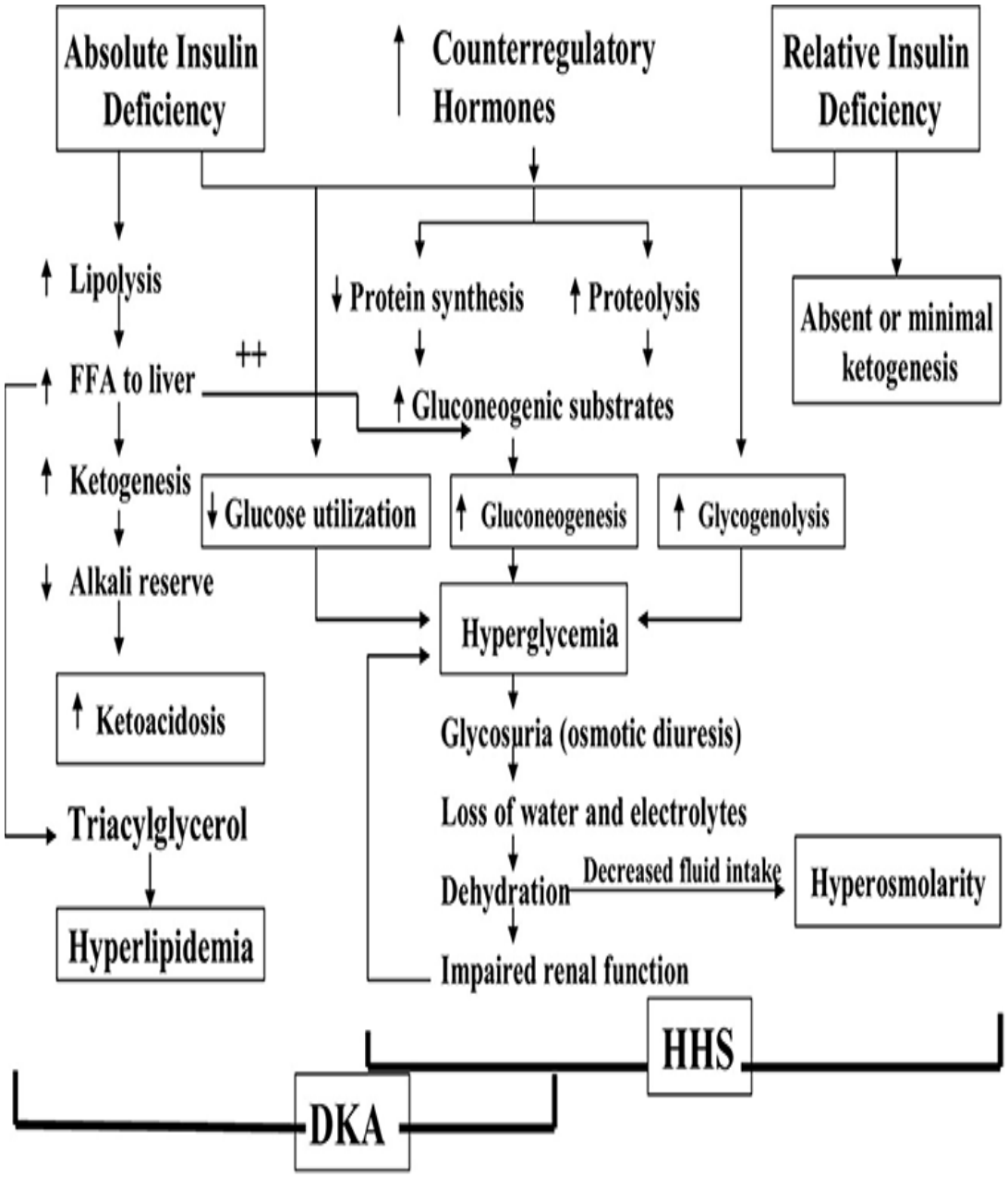
The altered insulin glucagon ratio facilitates hepatic gluconeogenesis. The excess counter regulatory hormones especially glucagon causes activation of beta oxidation of fatty acids. This produces acetyl co A via the ketogenic pathway. Products of this pathway include the ketone bodies which produce ketosis and acidosis. The ketone bodies are acetone, beta hydroxyl butyrate and aceto acetate. The ensuing acidosis is detrimental to the tissues of the heart and central nervous system. DKA can result in osmotic diuresis induced severe dehydration also.

Dka can be associated with hyponatremia due to the osmotic diuretic effect of glucose as well as the excretion of cations along with the negatively charged ketone bodies. Hypokalemia can occur due to the osmotic diuretic effect as well as gastrointestinal losses associated with vomiting.

HHS

Hyperosmolar hyperglycemic syndrome, previously known as the hyperosmolar nonketotic syndrome occurs due to the elevated glucose levels and volume depletion. It is secondary to osmotic diuresis and hyper osmolality. It has a significant mortalityrate. It is often precipitated by infection, alcohol, myocardial infarction and drugs like diuretics. HHS can lead onto coma, seizures and renal failure. It is treated with half normal saline, insulin, electrolyte repletion and treatment of the underlying cause.

The following picture shows the pathophysiology of diabetic keto acidosis and hyper osmolar hyperglycaemic states



HYPOGLYCEMIA

Hypoglycemia is often secondary to drugs used in management of diabetes. Hypoglycaemia refers to a state of low blood glucose level < 50 mg

Clinical symptoms of hypoglycemia

Sympathetic/parasympathetic activation	Neuroglycopenia
A. Clinical signs and symptoms of adrenergic activation Pallor, tremor, palpitations and anxiety Acute sensation of hunger Occasionally hypothermia, vomiting, fever, moderate tachycardia, crises of systolic hypertension *B. Clinical signs and symptoms of parasympathetic activation* Nausea and eructation Cold sweating Mitigation of expected tachycardia or true bradycardia Mild hypotension	*Clinical signs and symptoms of neuroglycopenia* Headache, dizziness, fatigue, irritability or apathy and lethargy Frequent yawning and perioral numbness Disturbed vision and diplopia Paresthesias and motor dysfunction Cognitive impairment, mental confusion and inebriation Personality changes, psychotic behavior Occasionally transient hemiparesis or focal neurologic deficits Convulsions (in children simulating true crises of epilepsy) Semi-coma, coma and even death

Short duration of low blood sugar level can manifest as giddiness, undue sweating, seizures etc. It may be treated with parenteral administration of glucose solution. Prolonged period leads to tissue damage and brain death.

CHRONIC COMPLICATIONS

The major chronic complications in diabetes mellitus are caused by the persistent elevated glucose levels as proved by that DCCT Trial. States of continuous hyperglycemia in association with hypertension, dyslipidemia, smoking , alcoholism , dietary habits, and environment factors can result in structural alterations which lead on to organ damage.

The chronic complications of diabetes are principally caused by the

- Vascular changes and the
- Metabolic changes associated with this disease.

The vascular changes in diabetes are as follows :

1. Diminished contractility of the vessels
2. Thickening of the basement membrane
3. Hypercoagulability due to alterations in levels of clotting factor 7 and von willebrand factor
4. Excess neo vascularisation

Chronic hyperglycemia may be associated with endothelial dysfunction which is secondary to imbalance between the factors that cause contractility and those that cause vasodilatation.

5. Serum fibrinogen levels are found to be elevated in diabetes and this may contribute to a procoagulant state. Also co-morbid condition like hypertension have been shown to accelerate the severity of chronic complications of diabetes; this was proven in the DCCT AND UKPDS trials. For every 10 mm Hg reduction of the systolic blood pressure, there is a 12% reduction in the risk of myocardial infarction.

The metabolic pathways and involved in diabetic complications are as follows

(a) Abnormalities in the aldose reductase pathway

(b) Diacylglycerol protein kinase pathway

(c) Activation formation of Advanced glycation end products (AGE)

(d) Synthesis of reactive oxygen species

MICRO VASCULAR COMPLICATIONS

DIABETIC RETINOPATHY

Some of the earliest changes noted in the retina of diabetic patients are

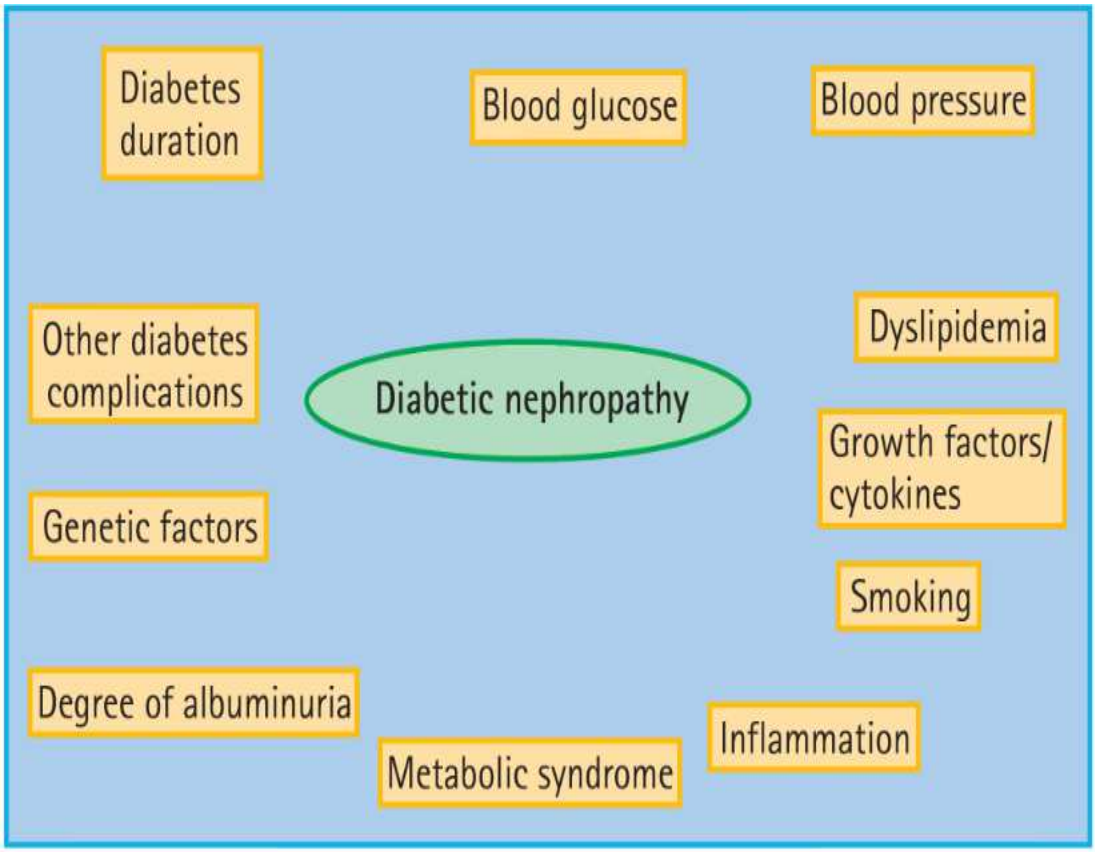
1. Micro aneurysms
2. Dot and blot haemorrhage
3. Chronic hypoxia can result in excess vascular tissue proliferation known as *neovascularisation*. But the newly formed blood vessels are highly permeable and prone for damage – leading to retinal and vitreous haemorrhages

DIABETIC NEUROPATHY

Diabetic neuropathy is due to the effect of advanced glycation end products and othet toxic compounds on the peripheral nerves. It can also be due to athero sclerosis of the vasa nervosum which supply the nerves.

DIABETIC NEPHROPATHY

One of the major complications of diabetes is diabetic nephropathy. It is characterised by the excretion of albumin in the urine in the early stages while in the later stages there is a progressive decline in the glomerular filtration rate , elevated creatinine and hypertension. The usual time period taken for the development of diabetic nephropathy from the onset of diabetes is around 15 to 20 years. Several factors contribute to the diabetic nephropathy as shown below



Histologically, the diabetic nephropathy is characterized by glomerular sclerosis and arterial hyalinization. Factors that determine the development of nephropathy are the duration of diabetes, severity of diabetes and the presence of comorbid conditions. It has been noted that diabetic population with a higher level of nocturnal diastolic blood pressure and loss of nocturnal diastolic dipping have greater degrees of micro albuminuria. Smoking and elevated blood lipid levels are also contributory factors for the development of albuminuria. Increased levels of mannose binding lectin have been shown to indicate the progression of albuminuria in diabetic patients

Diabetic nephropathy is a leading cause of end stage renal disease in both types of diabetes. Diabetic nephropathy been noted to occur in about 35 % of patients who have diabetes. Racial factors, positive family history , low birth weight and comorbid conditions like hypertension, dyslipidemia , smoking etc add to the risk of nephropathy in the diabetic patients. Genes responsible for diabetic nephropathy are assumed to be located on chromosomes 7p & 18 q. Other contributory factors are dietary indiscretion and elevated uric acid levels.

PATHOGENESIS OF DIABETIC NEPHROPATHY

Structural alterations in the afferent vessels and glomerular hyperfiltration are associated with shear stress and increased local cytokine production. Cells in the glomeruli and mesangium undergo proliferation due to the growth promoting effects of insulin like growth factor (IGF1), epidermal growth factor (EGF), platelet derived growth factor, vascular endothelial growth factor (VEGF), transforming growth (TGF) and nitric oxide.

The renal histology in diabetic nephropathy shows nodular glomerulosclerosis (also called Kimmelstiel Wilson lesion) and glomerular sclerosis. Thickening of the basement membrane occurs. Inflammatory cells like the monocytes, macrophages and T Lymphocytes are attracted to the glomeruli by the chemotactic cytokines. Alterations in the structure of the glomerular basement membrane and reduction of the negatively charged heparan sulfate contribute to the increased glomerular permeability. In the early stages there is selective excretion of low molecular weight proteins like albumin. However in later stages, even high molecular weight proteins breach the basal lamina and get excreted in urine. Tubulointerstitial damage is also noted in diabetic nephropathy.

Pro-apoptotic genes are expressed in the tubules l due to the effect of Angiotensin II. Epithelial to mesenchymal transition cause conversion of epithelial cells to interstitial fibroblasts. These cells cause increased matrix production and alteration of the basement membrane.

Anaemia is an important contributor to diabetic nephropathy. Anaemia may result in renal hypoxia which induces inflammation and subsequent renal damage.

Glycemic status has been noted to correlate well with the degree of diabetic nephropathy. Risk of diabetic nephropathy is low when HBA1c levels are less than 7 %.

STAGES OF DIABETIC NEPHROPATHY

Micro albuminuria is defined as the excretion of 30 to 300 milligrams of albumin for 24 hours in at least 2 of 3 consecutive non-ketotic sterile urine samples. Low grades of albumin excretion are not detected by the routine test for protein (example biuret test). Instead they have to be detected by dipstick method, Enzyme linked immune assays , nephelometry or radioimmunoassay. Spot urine samples may be used to detect albumin excretion. However confounding factors such as severe physical exertion, urinary tract infections , non diabetic diseases of the kidneys and hematuria have to be ruled out.

Albuminuria more than 300 milligram per day constitutes diabetic nephropathy. The earliest change of renal function in diabetes is hyper filtration or increase in the glomerular filtration rate. Then there is a gradual onset of albuminuria. If the patient excretes less than 30 milligram of albumin per day , it is known as normo-albuminuria. Excretion of albumin at a rate of 30 to 300 milligrams per day is known as micro albuminuria. Onset of micro albuminuria accelerates the development of full blown diabetic nephropathy.

Stages of diabetic nephropathy are depicted in the following picture

Stage	GFR	UAE	Blood pressure	Years
1. Hyperfiltration	Super normal	<30 mg/day	Normal	0 - 5
2. Microalbuminuria	High normal - normal	30 - 300 mg/day	Rising	5 - 15
3. Overt proteinuria	Normal - decreasing	>300 mg/day	Elevated	10 - 20
4. Progressive nephropathy	Decreasing	Increasing	Elevated	15 - 25
5. ESKD	<15 mL/min	Massive	Elevated	20 - 30

ESKD = end-stage renal disease; GFR = glomerular filtration rate; UAE = urinary albumin excretion.

ALTERED METABOLIC PATHWAYS IN DIABETIC NEPHROPATHY

PROTEIN KINASE C PATHWAY

Elevated glucose levels have been associated with activation of the protein kinase C cascade, which can contribute to accumulation of the extracellular matrix

ADVANCED GLYCATION END PRODUCTS

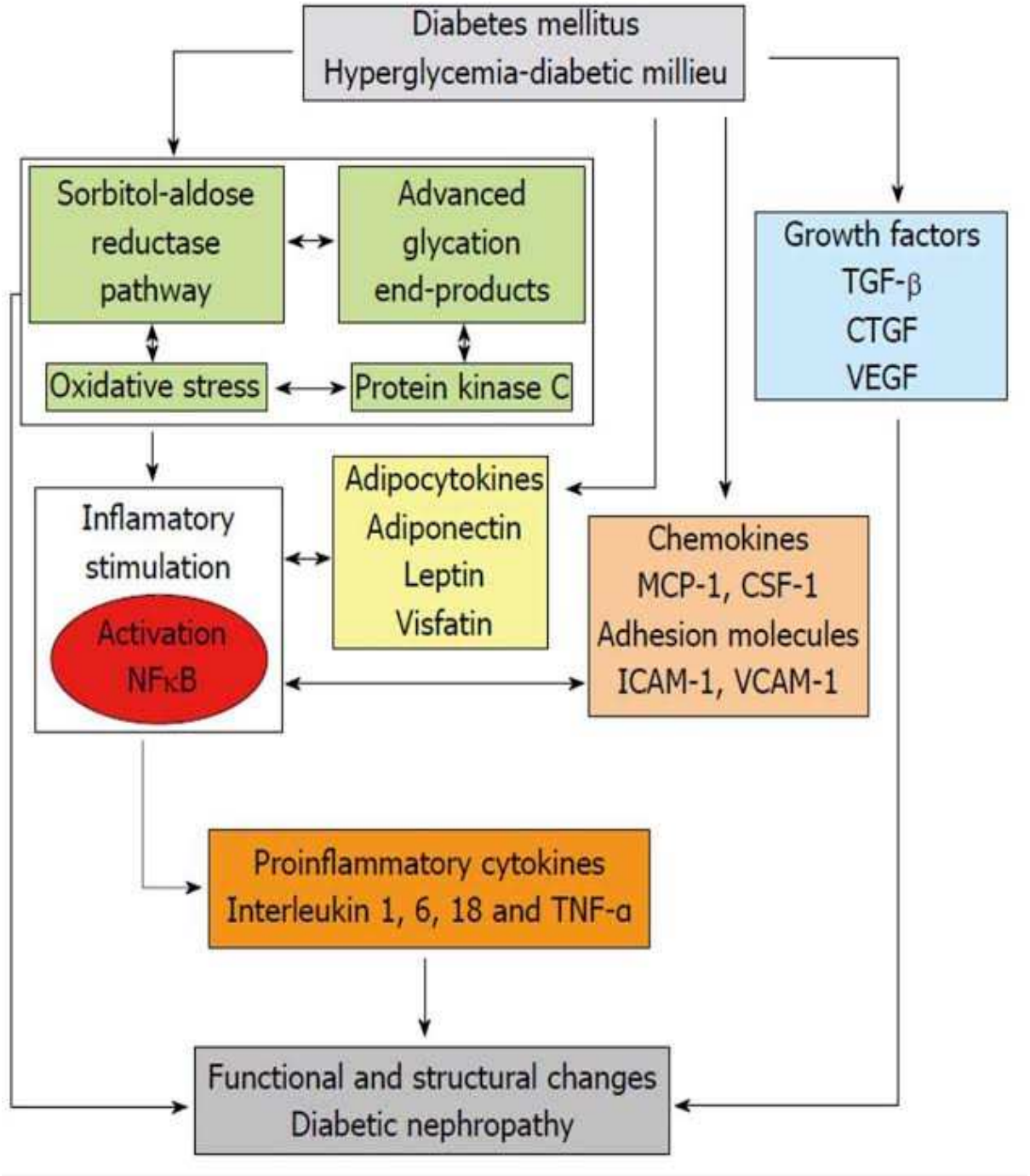
Several advanced glycation end products have been identified in diabetic people. These directly and indirectly cause cellular hypertrophy and inhibition of the nitric oxide pathway. Such changes ultimately produce albuminuria and sclerosis of the glomeruli. AGEs can also cause podocytopathy.

POLYOL PATHWAY

This pathway mediates the conversion of glucose to sorbitol and fructose.

The enzyme aldose reductase is responsible for the conversion. Sorbitol can alter the extracellular matrix and basement membrane scaffolds.

PATHOGENESIS OF DIABETIC NEPHROPATHY



HEXOSAMINE PATHWAY

The hexosamine pathway converts glucose to N-acetylglucosamine. This causes increased transcription of SP-1 protein and subsequently Transforming Growth Factor beta (TGF B) and Plasminogen Activator Inhibitor, which cause renal damage

RAAS PATHWAY

Renin angiotensin aldosterone axis is found to be in a activated state in diabetic patients. Advanced glycation end products and reactive oxygen species also directly stimulate the angiotensin production. Angiotensinogen is converted to Angiotensin II which results in cellular hypertrophy, matrix expansion and local cytokine production all of which terminate in renal damage.

OTHER PATHWAYS

Adenosine monophosphate activated protein kinase pathway is also altered in diabetic nephropathy

Elevated uric acid can contribute to the pre existing nephropathy in diabetic population due to its oxidative damage.

DIABETIC NEPHROPATHY – CORRELATION WITH RETINOPATHY AND CARDIO VASCULAR OUTCOME

Diabetic nephropathy and retinopathy have a close relationship. Almost every patient with Type 1 Diabetes and nephropathy will have diabetic retinopathy. However only 50-60 % of type 2 diabetic nephropathy patients will have retinopathy.

The onset of diabetic nephropathy can reduce the lifespan of diabetic patients since it heralds End stage renal disease (ESRD) as well as adverse cardio vascular outcomes in these patients. Urinary albumin excretion is an excellent predictor of the cardiovascular outcomes in diabetic nephropathy patients. Albuminuria is associated with endothelial dysfunction and accelerated atherogenesis in such patients.

Hence it is mandatory to screen the fundus for retinopathic changes in these patients. They should also be subjected to a thorough cardio vascular evaluation. Peripheral neuropathy, especially autonomic neuropathy is often an accompaniment to the nephropathy in these patient.

EVALUATION OF A CASE OF DIABETIC NEPHROPATHY

Every diabetic nephropathy patient should be evaluated for the following:

1. Measurement of urinary albumin and protein
2. Measurement of serum creatinine clearance and estimation of glomerular filtration rate
3. Management of blood pressure
4. Ophthalmological evaluation
5. Cardiac evaluation

Micro albuminuria predicts a poor renal and cardiovascular outcome and hence is an indicator for targeted treatment. Overt diabetic nephropathy represents a stage of microalbuminuria characterized by daily albumin excretion of more than 300 milligram per day

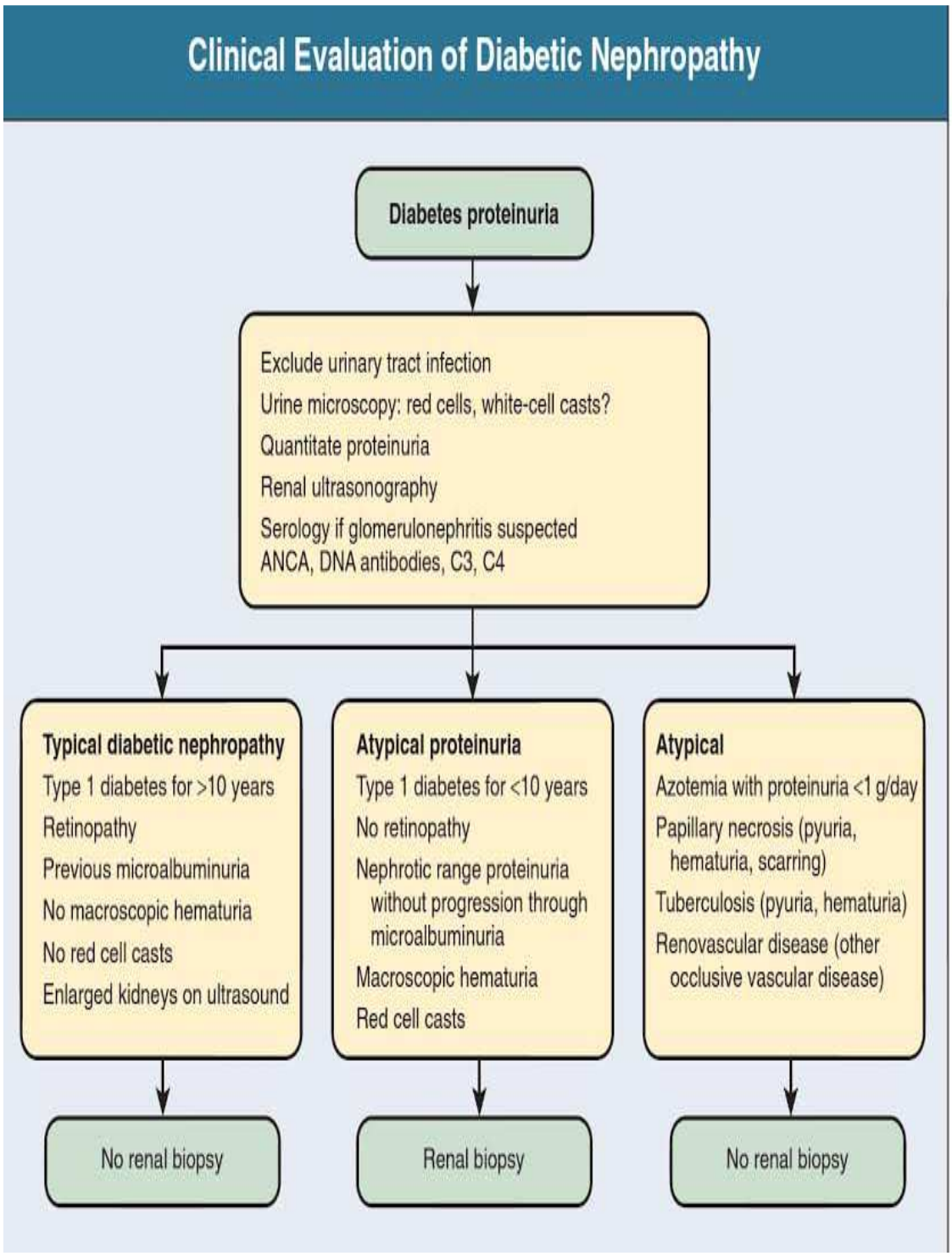
DIFFERENTIAL DIAGNOSIS FOR DIABETIC NEPHROPATHY

- Hematuria
- Nephritic syndromes
- Membranous nephropathy
- Focal segmental glomerulosclerosis
- Acute interstitial nephritis
- Post infectious glomerulo nephritis
- IgA nephropathy

RENAL BIOPSY MAY BE INDICATED IN DIABETIC NEPHROPATHY IN THE FOLLOWING SITUATIONS

- Sudden severe proteinuria
- Microscopic hematuria
- Nephritic urinary sediment
- Rapidly progressive renal disease

Approach to a case of diabetic nephropathy is as follows :



The other complications are

1. Necrobiosis lipoidica diabeticorum
2. Diabetic dermopathy
3. Cheiro arthropathy
4. Charcot joints
5. Foot problems
6. Sexual dysfunction
7. Gastroparesis
8. Psychological disorders like cognitive disorders, adjustment disorder
9. Infectious complications

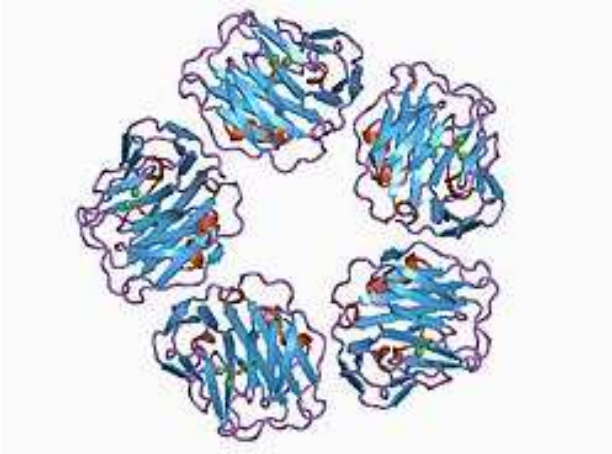
C REACTIVE PROTEIN

Early stages of inflammation are characterized by acute phase reactions mediated by the acute phase proteins synthesised by the liver. The inflammatory cytokines induce the synthesis of acute phase reactants

One of the important acute phase reactants is C reactive protein. It is a very good indicator of the severity of inflammation. It is called a C-reactive protein because it was noted to bind avidly to the capsular polysaccharide of bacterial cell wall.

STRUCTURE OF C REACTIVE PROTEIN

It is a pentaxin family molecule. It is composed of five polypeptide subunits. Each of the subunits contain about 200 amino acid residues. They have a cyclical pentameric structure as shown below



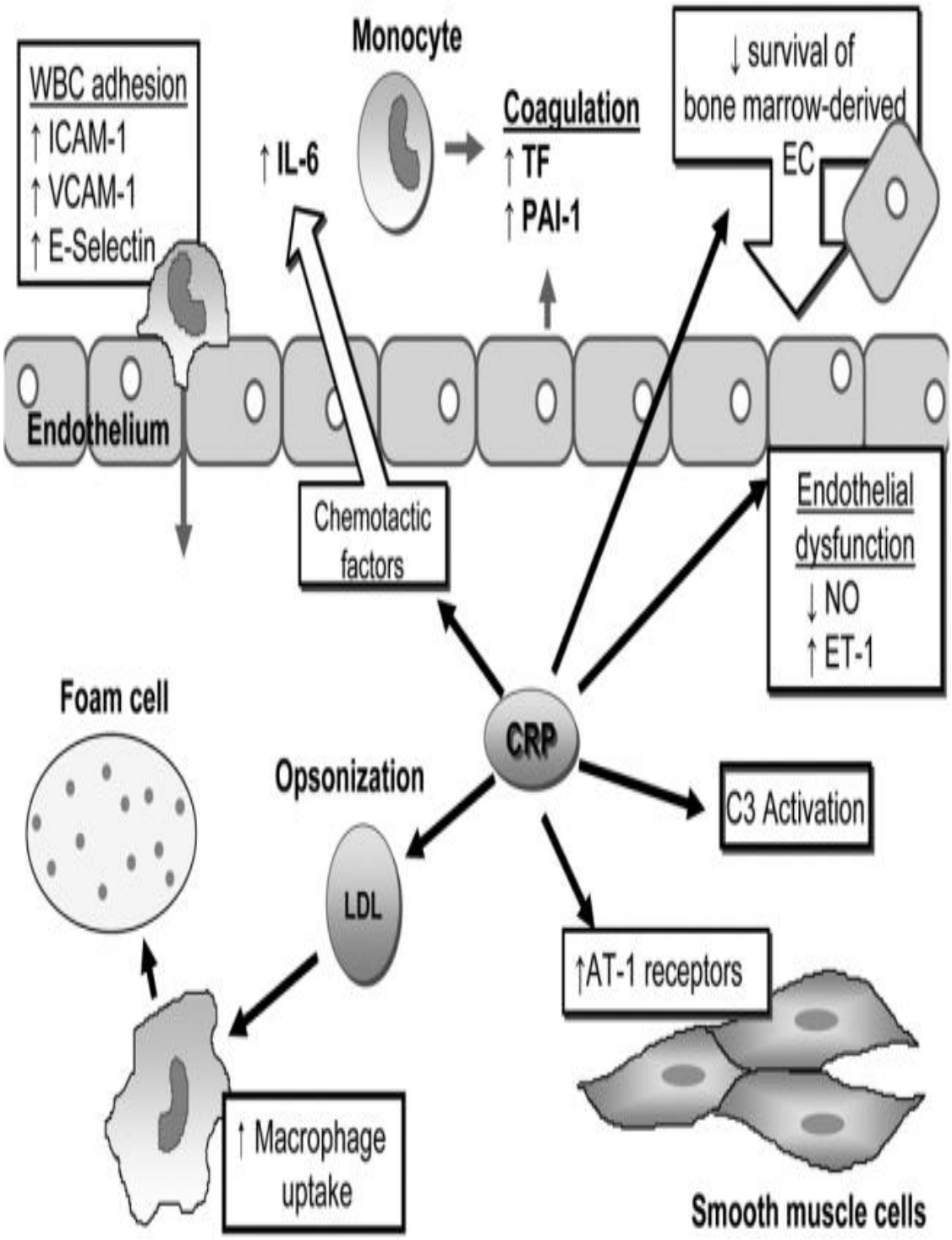
EFFECTS OF CREACTIVE PROTEIN

The predominant site of synthesis of CRP is the liver. The usual level is about 0.1mg% . However inflammatory states can cause several fold elevation of CRP. It is noted to be elevated on the third day of inflammation and its falls to near normal levels within about 24 hours after the inflammation subsides. But it should also be kept in mind that CRP levels may be altered by diet, smoking, hypertension, increased BMI, poor sleep, alcoholism etc.

Usual conditions associated with high CRP are those that are associated with chronic inflammation namely rheumatoid arthritis, tuberculosis and neoplasms. Higher CRP levels have also been noted to be associated with certain chronic conditions like coronary artery disease, diabetes mellitus and hypertension. Value more than 10 to 12 mg% of serum CRP is considered to indicate a severe inflammation.

The physiological role of CRP is not known. However it is presumed that, CRP binds to the phosphoproteins, fibronectin, and histones which enter the circulation during the cellular apoptosis and CRP may facilitate their elimination. CRP can act as a bridge between innate and acquired immunity. It can bind to the constant position of antibodies and thereby activate the classical complement pathway.

Following pictures shows the function of CRP



CRP can also activate the complement pathway due to its interaction with C1q and C3 molecules. It can activate the membrane attack complex and it activates the alternate complement cascade through binding with factor H. CRP can directly induce a cytokine cascade, which can contribute to the inflammatory tissue damage.

CRP does is used as a valuable indicator of inflammation due to the following factors

(a) It Rises early with inflammation

(b) The degree of rise is proportional to the severity of inflammation.

(c) CRP may not vary significantly with age and sex

(d) CRP estimation is standardized and lab to lab variations are minimal.

FIBRINOGEN

Fibrinogen is a soluble plasma protein that helps in the coagulation pathway. It is synthesised by the liver and released into the circulation. Whenever the blood vessel or endothelium is damaged, a platelet plug is formed and then clotting factors are activated. All these processes culminate in the conversion of fibrinogen to fibrin. Fibrin forms the clot which secures hemostasis. The normal value is 150 to 400 mg / dl. Since it is an acute phase reactant it is likely to be elevated in inflammatory and acute stressful states.

Conditions associated with elevation of fibrinogen are as follows :

1. Severe inflammation
2. Tissue damage
3. Sepsis
4. Malignancy
5. Acute coronary events
6. Stroke
7. Rheumatoid arthritis

Studies have shown that diabetic nephropathy is a pro inflammatory state and hence serum fibrinogen which is an acute phase reactant is elevated. The degree of elevation of serum fibrinogen is noted to correlate with the severity of nephropathy

C-REACTIVE PROTEIN & SERUM FIBRINOGEN IN DIABETIC NEPHROPATHY

C-reactive protein, an inflammatory marker has an excellent correlation with adverse cardiovascular outcomes. CRP levels are noted to be increased in people with diabetes, especially so in those with diabetic nephropathy. It is proposed that diabetes may be associated with a long term immune system activation and chronic inflammatory state. Hence acute phase reactants namely C reactive protein, serum amyloid protein, interleukins and fibrinogen are all noted to be elevated in the diabetic population. The advanced glycation end products may alter the intracellular signalling and gene expression as a result of which the inflammatory responses become altered. A pro inflammatory state ensues, with associated elevation of acute phase.

MATERIALS AND METHODS

MATERIALS AND METHODS

Aims and Objectives

To study the co-relation between levels of acute phase reactants (serum CRP , serum fibrinogen) and severity of albuminuria in patients admitted with type 2 diabetes mellitus.

Study center

Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai

Duration of study

6 months

Study design

Observational Study

Sample size

100 patients

Inclusion criteria

1. Patients with Type 2 Diabetes mellitus (less than 10 years of duration) attending the OPD
2. Age : less than 50 years

Exclusion criteria

- Patients with current or recent (< 1 week) infectious diseases (UTI,LRI , sepsis , AGE , viral fever etc)
- Patients with cancer
- Patients with uncontrolled hypertension (> 160/90)
- Smokers
- Known cases of immunological disorders
- Patients with clinical history of cardiovascular diseases
- Pregnancy
- Patients with known history of CVA , CAD
- Known cases of CKD

Data collection and methods

Patients are subjected to detailed history taking and clinical examination.

Materials and methods

100 Patients with type 2 diabetes mellitus, attending the OPD are selected for clinical study as per inclusion / exclusion criteria and are subjected to clinical assessment (BMI, Waist hip ratio, blood pressure) and laboratory evaluation (serum CRP, serum fibrinogen, serum creatinine , fasting plasma glucose , 24 hours urinary albumin excretion).

Routine investigations (complete blood counts, urine routine, electrocardiogram, chest X ray, ultrasound abdomen) are also done.

Procedure / Investigation Details

1. Serum Creatinine	:	Calorimetric method
2. Plasma fasting glucose	:	Automated enzyme method
3. 24 hrs urine albumin	:	Turbidimetry
4. Serum CRP	:	Immuno assay
5. Serum fibrinogen	:	Automated enzyme method

Analysis plan

SPSS - epi info software

Sponsorship

No

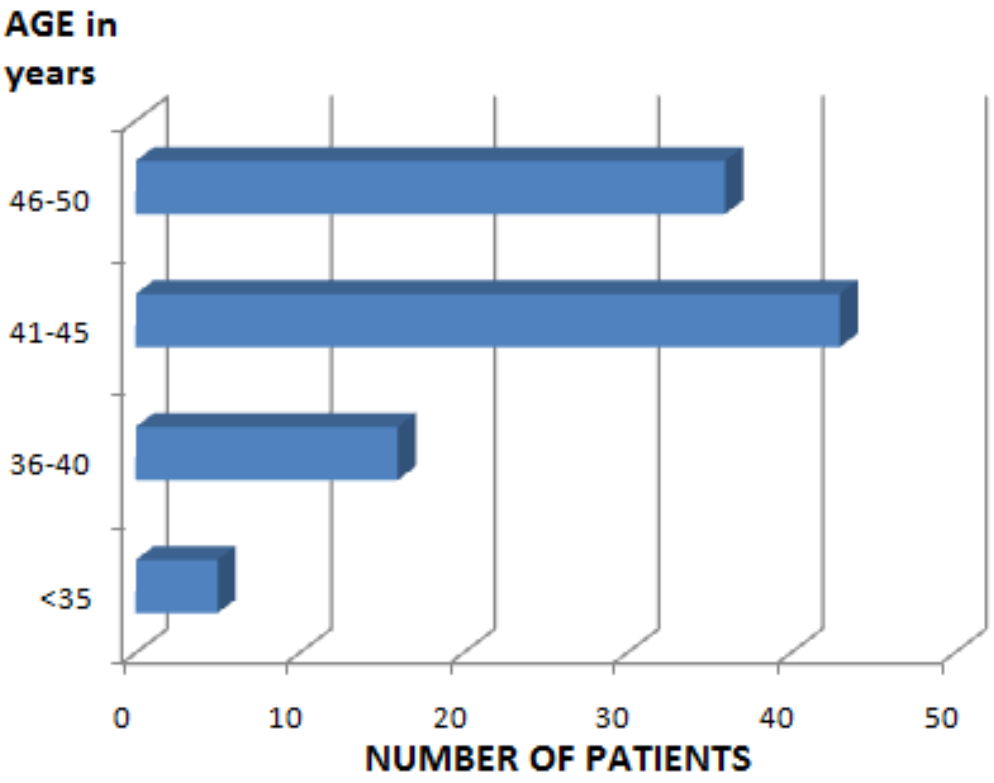
Conflict of interest

None

OBSERVATIONS AND RESULTS

OBSERVATIONS AND RESULTS

AGE DISTRIBUTION OF THE PATIENTS IN THE STUDY

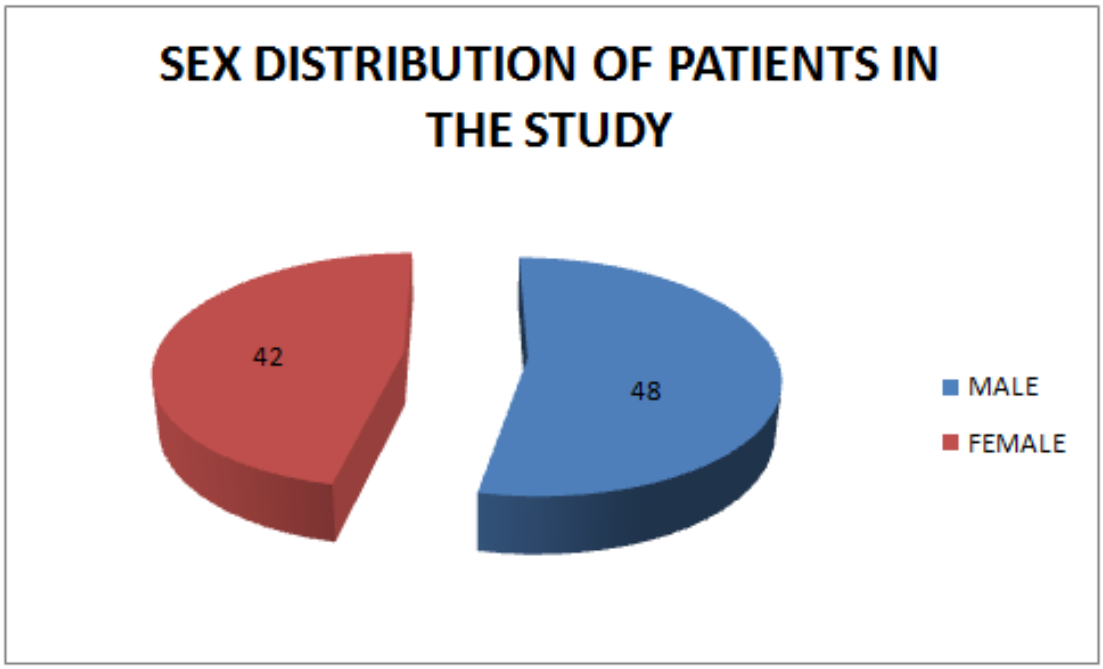


A total of 100 patients were included in the study.

The age groups < 35 years, 36-40 years, 41-45 years and 46-50 years contained 5, 16, 43 and 36 numbers of patients respectively

GENDER WISE DISTRIBUTION OF THE PATIENTS

IN THE STUDY



The study included 42 males and 48 females.

COMPARISON OF MULTIPLE PARAMETERS BETWEEN NORMO ALBUMINURIC GROUP AND MICRO/OVERT ALBUMINURIC GROUP

	URINE ACR	N	Mean	Std. Deviation	Std. Error Mean	t value	P value
SYSTOLIC BP	>= 30.00 Abnormal	70	132.8857	22.41024	2.67854	1.709	0.092
	< 30.00 Normal	30	126.0000	16.49242	3.01109		
DIASTOLIC BP	>= 30.00 Abnormal	70	84.8857	12.32241	1.47281	3.321*	0.001
	< 30.00 Normal	30	78.0667	7.83420	1.43032		
BMI	>= 30.00 Abnormal	70	25.9457	4.52294	.54060	3.581*	0.001
	< 30.00 Normal	30	23.3567	2.62897	.47998		
FBS	>= 30.00 Abnormal	70	142.9429	39.52320	4.72393	1.946	0.06
	< 30.00 Normal	30	129.6667	26.95889	4.92200		
HBA1C	>= 30.00 Abnormal	70	7.0757	1.45138	.17347	4.248*	p<0.001
	< 30.00 Normal	30	6.2000	.61026	.11142		
CRP	>= 30.00 Abnormal	70	11.6429	6.89473	.82408	2.197*	0.031
	< 30.00 Normal	30	8.9333	5.02362	.91718		
FIBRINOGEN	>= 30.00 Abnormal	70	320.2714	111.97618	13.38371	4.42	p<0.001
	< 30.00 Normal	30	246.3667	54.90210	10.02371		
SR.CREATININE	>= 30.00 Abnormal	70	1.3571	.65199	.07793	5.125*	p<0.001
	< 30.00 Normal	30	.8500	.33399	.06098		

This table shows that systolic BP did not correlate with degree of albuminuria (p value =0.092) , but the diastolic BP shows a good correlation with severity of albuminuria (p value =0.001)

A higher BMI was noted to be associated with a higher degree of albuminuria (p value =0.001)

Fasting blood sugar did not show a correlation with albuminuria (p value =0.06)

HBA1C correlates with excretion of albumin as shown by the p value of 0.001

Higher albumin excretion rates are associated with higher levels of CRP (p value =0.031)

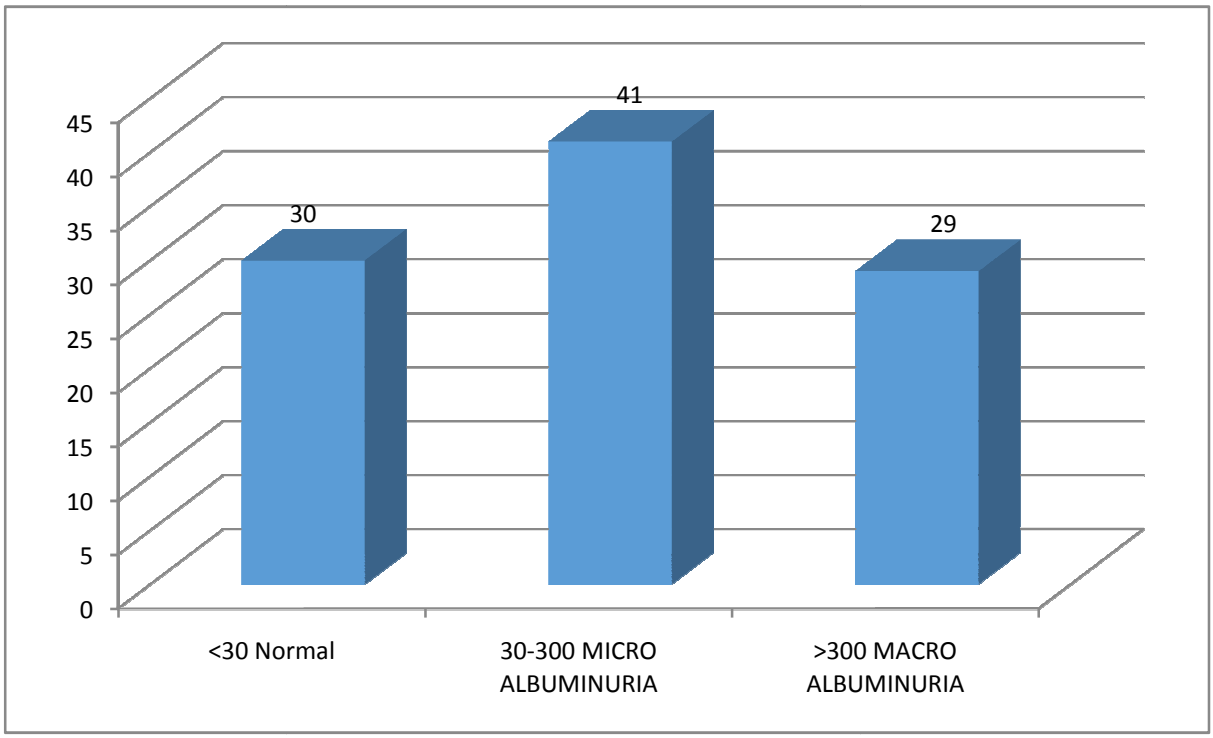
Higher albumin excretion rates are associated with higher levels of Sr.Fibrinogen (p value =0.001)

Albuminuria grade correlates with serum creatinine values (p value = 0.001)

ALBUMINURIA CLASSES IN THE STUDY

The following table shows the correlation between sex and grades of albuminuria

Urine_ACR_class * SEX Cross tabulation				
Urine_acr_class		SEX		Total
		Male	Female	
<30 Normal	Count	17	13	30
	% within Urine_acr_class	56.7%	43.3%	100.0%
30-300 MICRO ALBUMINURIA	Count	24	17	41
	% within Urine_acr_class	58.5%	41.5%	100.0%
>300 MACRO ALBUMINURIA	Count	17	12	29
	% within Urine_acr_class	58.6%	41.4%	100.0%
Total	Count	58	42	100
	% within Urine_acr_class	58.0%	42.0%	100.0%



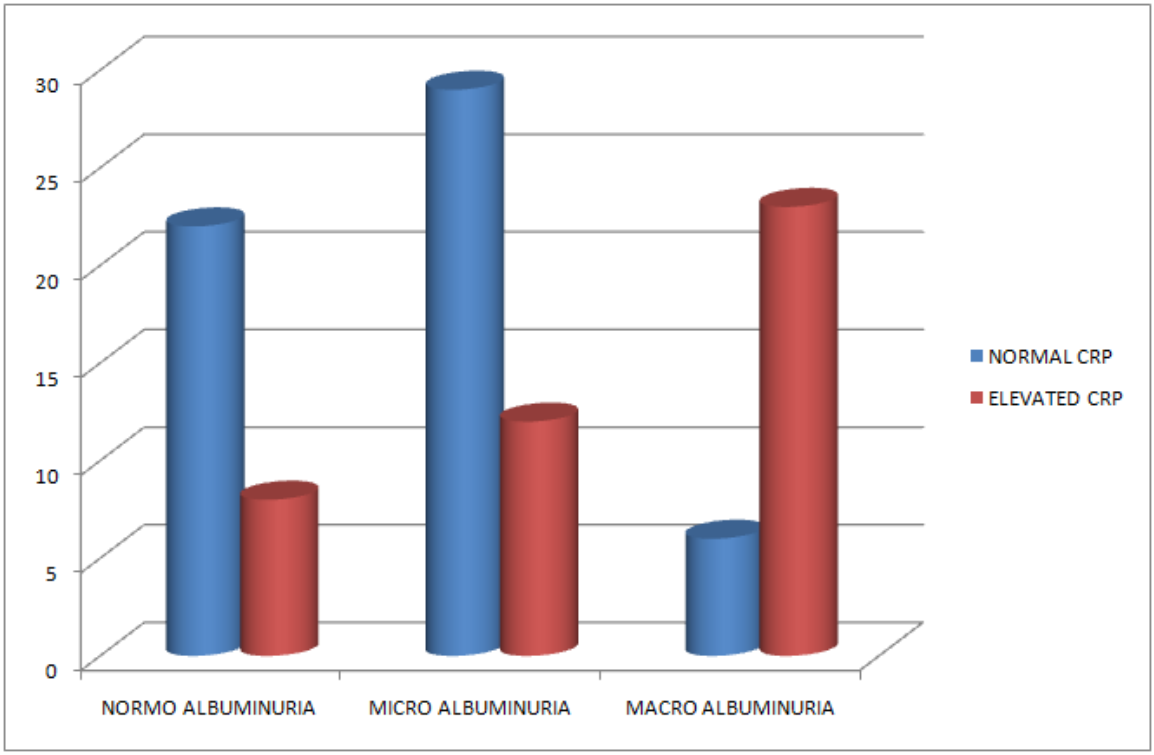
In our study, 30 patients belonged to the normo albuminuric group while 41 belonged to the micro albuminuric group and 29 belonged to the macro albuminuric groups.

CORRELATION BETWEEN GRADE OF ALBUMINURIA AND LEVELS OF C-REACTIVE PROTEIN

The following table shows the correlation between grade of albuminuria and levels of c-reactive protein

Crosstab				
Urine_acr_class		CRP_CLASS		Total
		NORMAL UPTO 10	ABNORMAL ABOVE 10	
<30 Normal	Count	22	8	30
	% within Urine_acr_class	73.3%	26.7%	100.0%
30-300 MICRO ALBUMINURIA	Count	29	12	41
	% within Urine_acr_class	70.7%	29.3%	100.0%
>300 MACRO ALBUMINURIA	Count	6	23	29
	% within Urine_acr_class	20.7%	79.3%	100.0%
Total	Count	57	43	100
	% within Urine_acr_class	57.0%	43.0%	100.0%

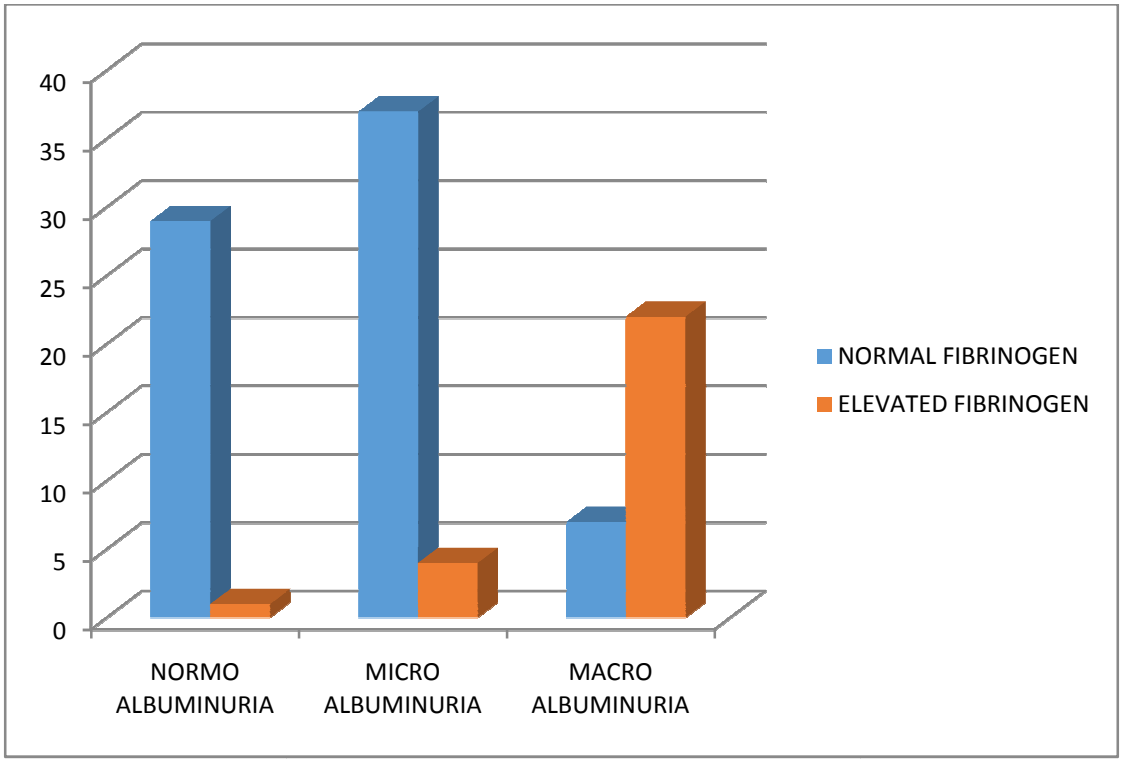
Chi-Square=22.019* p<0.001



This chart indicates that micro albuminuria and macro albuminuria are associated with higher levels of CRP when compared to the normo albuminuric patients.

CORRELATION BETWEEN GRADE OF ALBUMINURIA AND LEVELS OF SERUM FIBRINOGEN

Urine_acr_class * FIBRINOGEN Crosstabulation				
Urine_acr_class		FIBRINOGEN		Total
		NORMAL UPTO 350	ABNORMAL ABOVE 350	
<30 Normal	Count	29	1	30
	% within Urine_acr_class	96.7%	3.3%	100.0%
30-300 MICRO ALBUMINURIA	Count	39	2	41
	% within Urine_acr_class	95.1%	4.9%	100.0%
>300 MACRO ALBUMINURIA	Count	7	22	29
	% within Urine_acr_class	24.1%	75.9%	100.0%
Total	Count	75	25	100
	% within Urine_acr_class	75.0%	25.0%	100.0%



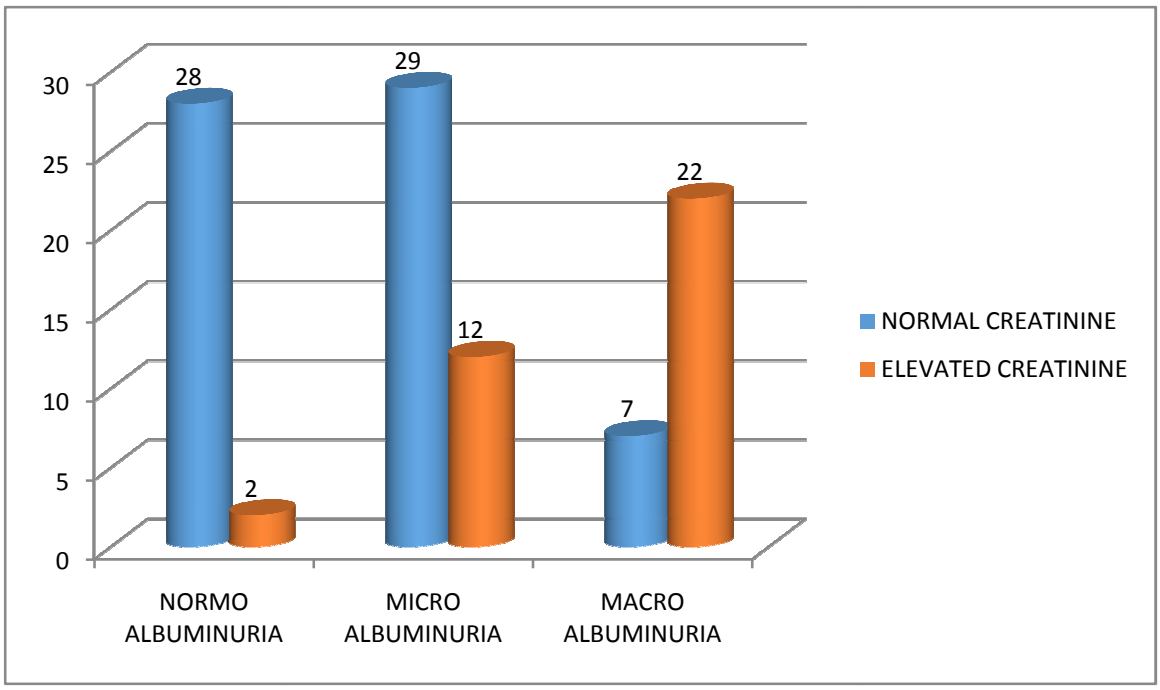
This table illustrates that serum fibrinogen is elevated in overt and macro albuminuric groups than normo albuminuric group.

CORRELATION BETWEEN GRADE OF ALBUMINURIA AND SERUM CREATININE

Crosstab

Urine_acr_class		SERUM_CREATININE		Total
		NORMAL UPTO 1.2	ABNORMAL ABOVE 1.2	
<30 Normal	Count	28	2	30
	% within Urine_acr_class	93.3%	6.7%	100.0%
30-300 MICRO ALBUMINURIA	Count	29	12	41
	% within Urine_acr_class	70.7%	29.3%	100.0%
>300 MACRO ALBUMINURIA	Count	7	22	29
	% within Urine_acr_class	24.1%	75.9%	100.0%
Total	Count	64	36	100
	% within Urine_acr_class	64.0%	36.0%	100.0%

Chi-Square=32.010* p<0.001

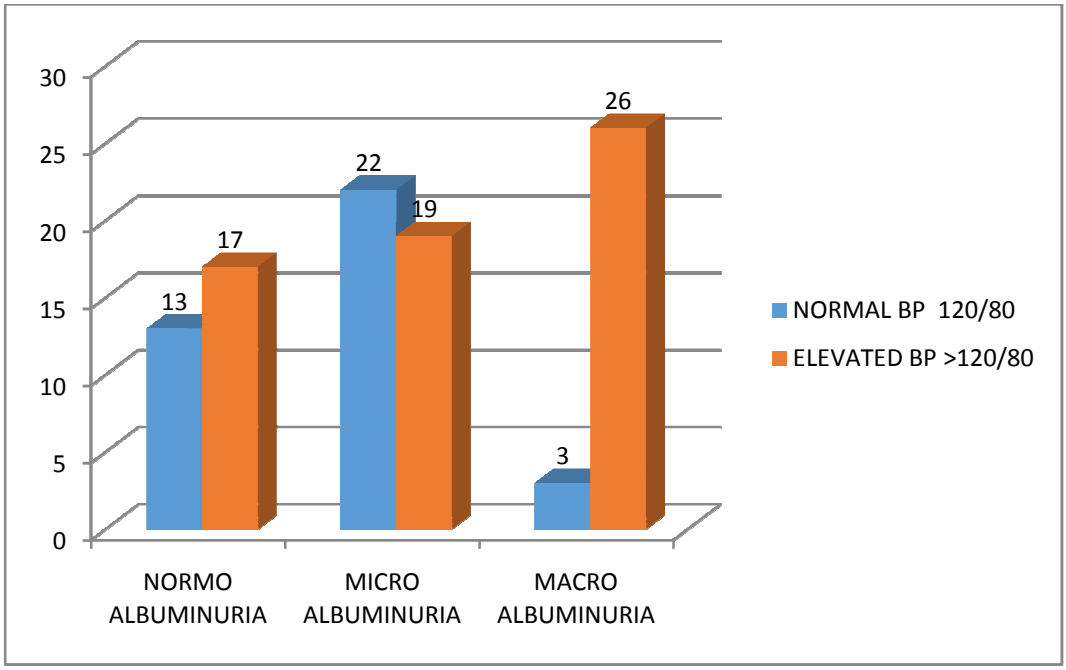


The above picture shows that higher levels of albumin excretion correspond to higher levels of serum creatinine. Thus albumin excretion in the urine is a good indicator of the glomerular filtration.

CORRELATION BETWEEN GRADE OF ALBUMINURIA AND BLOOD PRESSURE

Crosstab

Urine_acr_class		BLOOD_PRESSURE		Total
		UPTO 120/80	ABOVE 120/80	
<30 Normal	Count	13	17	30
	% within Urine_acr_class	43.3%	56.7%	100.0%
30-300 MICRO ALBUMINURIA	Count	22	19	41
	% within Urine_acr_class	53.7%	46.3%	100.0%
>300 MACRO ALBUMINURIA	Count	3	26	29
	% within Urine_acr_class	10.3%	89.7%	100.0%
Total	Count	38	62	100
	% within Urine_acr_class	38.0%	62.0%	100.0%



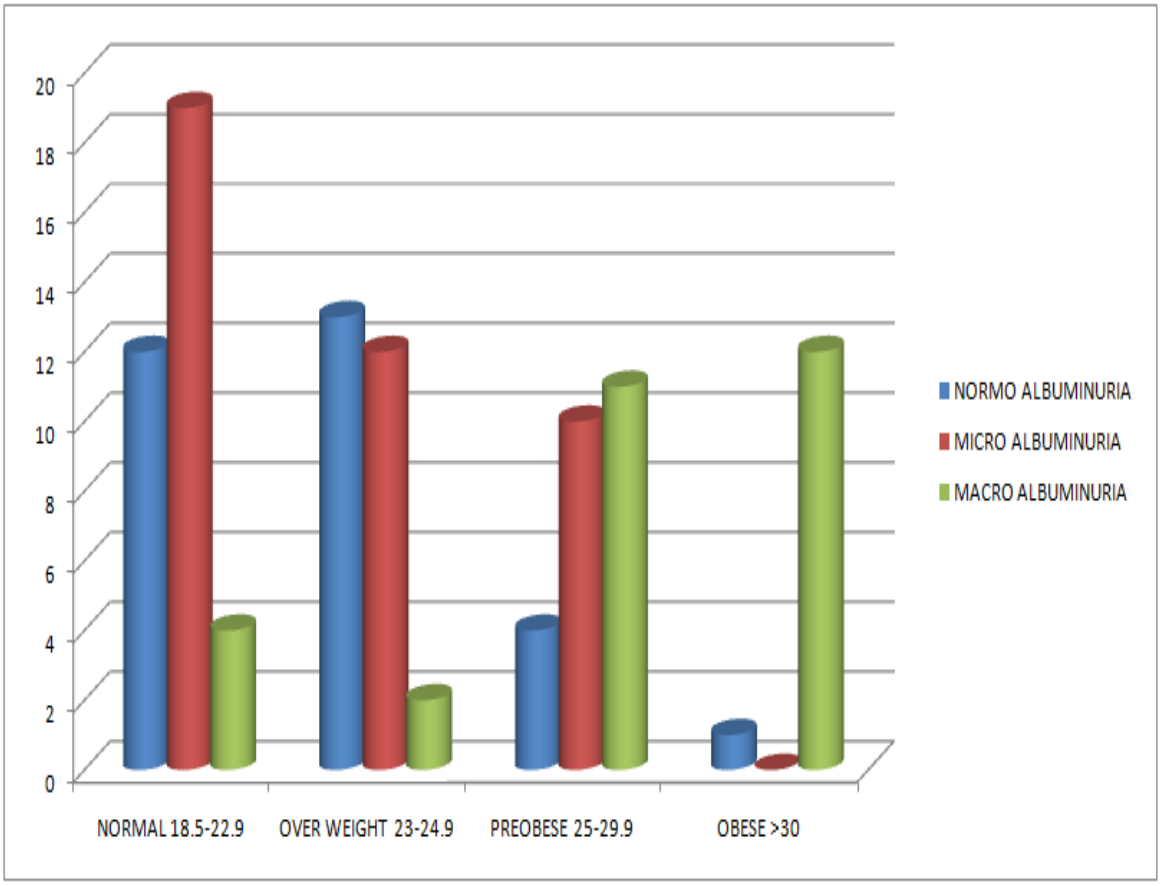
The above graph shows that higher blood pressures in diabetics are associated with greater albuminuria. Thus hypertension is an important contributor to the diabetic nephropathy. A direct comparison by means of Chi square indicated that diastolic bp correlates well with albuminuria , but systolic bp does not correlate to it.

CORRELATION BETWEEN GRADE OF

ALBUMINURIA ANDBODY MASS INDEX

Crosstab

Urine_acr_class		BMI_CLASS				Total
		18.5-22.9 NORMAL	23-24.9 OVERWEIGHT	25-29.9 PRE OBESE	ABOVE 29.9 OBESE	
<30 Normal	Count	12	13	4	1	30
	% within Urine_acr_class	40.0%	43.3%	13.3%	3.3%	100.0%
30-300 MICRO ALBUMINURIA	Count	19	12	10	0	41
	% within Urine_acr_class	46.3%	29.3%	24.4%	0.0%	100.0%
>300 MACRO ALBUMINURIA	Count	4	2	11	12	29
	% within Urine_acr_class	13.8%	6.9%	37.9%	41.4%	100.0%
Total	Count	35	27	25	13	100
	% within Urine_acr_class	35.0%	27.0%	25.0%	13.0%	100.0%



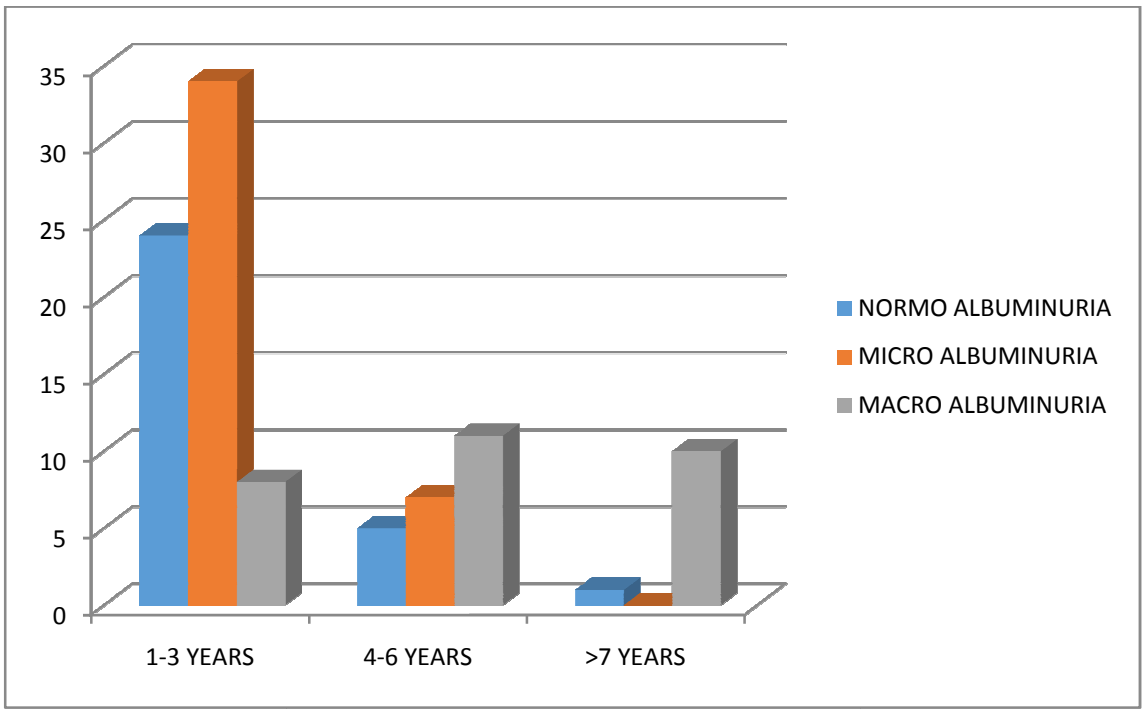
This chart shows that a higher body mass index is associated with greater degrees of diabetic nephropathy. Thus obese patients are more prone to develop renal complications of diabetes.

CORRELATION BETWEEN GRADE OF ALBUMINURIA AND DURATION OF DIABETES

Crosstab

Urine_acr_class		DURATION_dm			Total
		1-3 YEARS	4-6 YEARS	ABOVE 7 YEARS	
<30 Normal	Count	24	5	1	30
	% within Urine_acr_class	80.0%	16.7%	3.3%	100.0%
30-300 MICRO ALBUMINURIA	Count	34	7	0	41
	% within Urine_acr_class	82.9%	17.1%	0.0%	100.0%
>300 MACRO ALBUMINURIA	Count	8	11	10	29
	% within Urine_acr_class	27.6%	37.9%	34.5%	100.0%
Total	Count	66	23	11	100
	% within Urine_acr_class	66.0%	23.0%	11.0%	100.0%

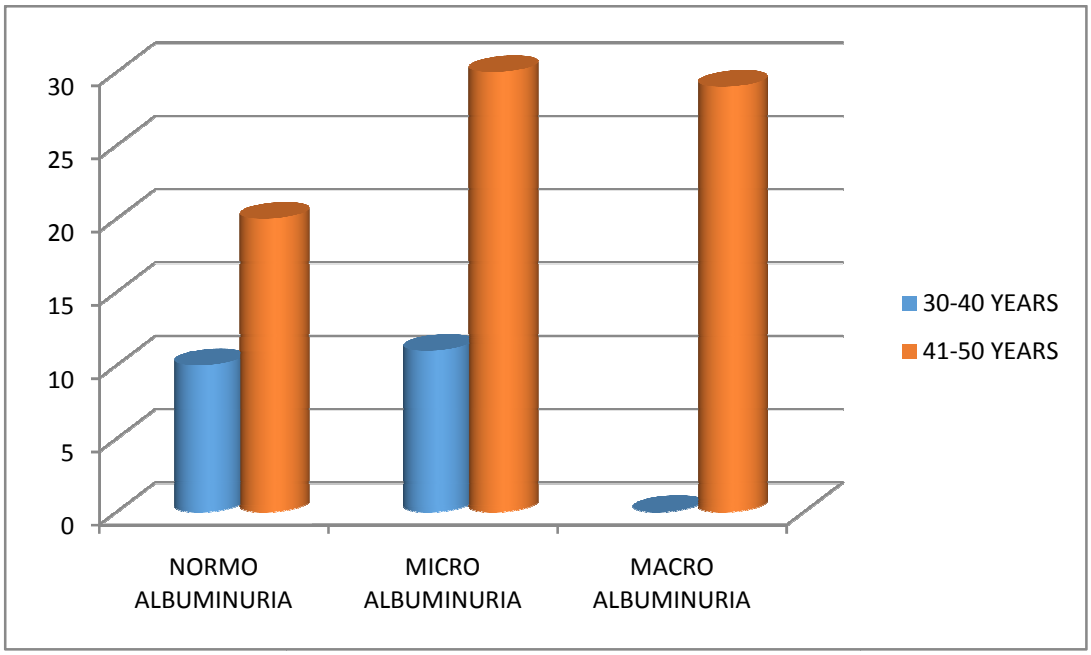
Chi-Square=33.766* p<0.001



The study included only people below 50 years of age , since age itself is a confounding factor for the two variables – CRP and fibrinogen.

Despite this limitation, the study shows that greater duration of diabetes is associated with greater degrees of albuminuria.

CORRELATION BETWEEN GRADE OF ALBUMINURIA AND AGE



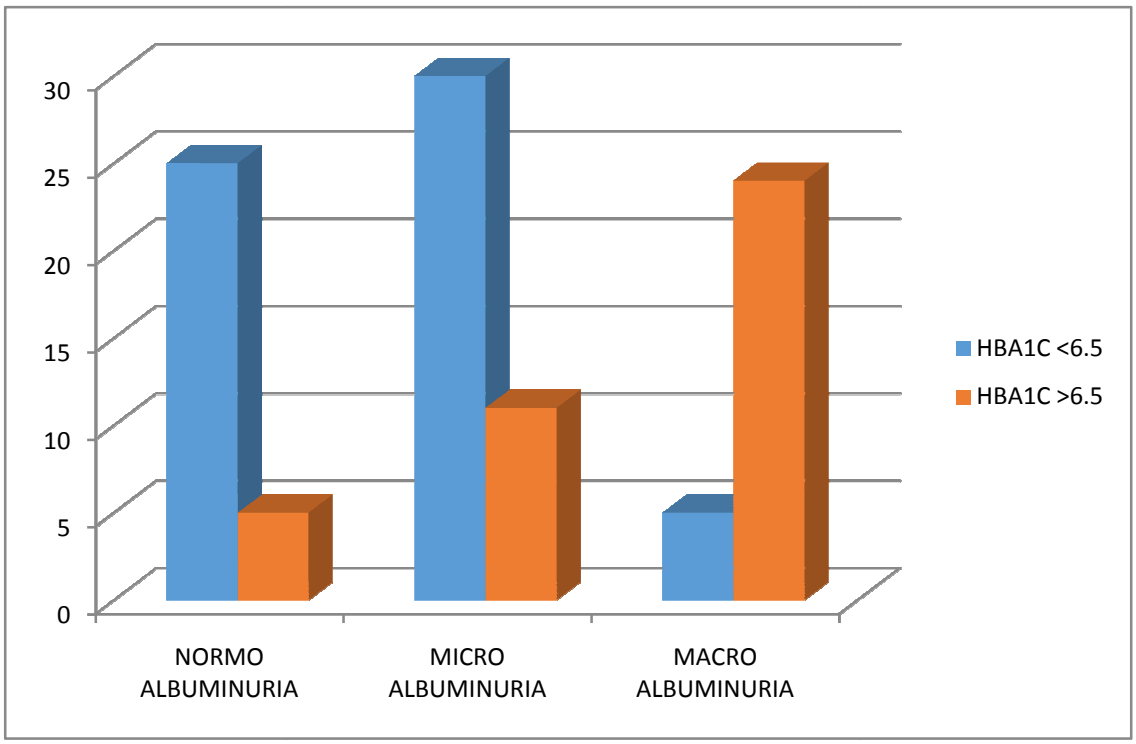
As already mentioned , the study inclusion criteria of only diabetic patients < 50 years – limits an accurate comparison of age with albuminuria. But still the above chart illustrates that micro and overt albuminuria are more likely in higher age groups.

CORRELATION BETWEEN GRADE OF ALBUMINURIA AND LEVELS OF HBA1C

Crosstab

Urine_acr_class		hba1c_class		Total
		<6.5 Normal	>6.5 Abnormal	
<30 Normal	Count	25	5	30
	% within Urine_acr_class	83.3%	16.7%	100.0%
30-300 MICRO ALBUMINURIA	Count	30	11	41
	% within Urine_acr_class	73.2%	26.8%	100.0%
>300 MACRO ALBUMINURIA	Count	5	24	29
	% within Urine_acr_class	17.2%	82.8%	100.0%
Total	Count	60	40	100
	% within Urine_acr_class	60.0%	40.0%	100.0%

Chi-Square=31.861* p<0.001



The micro and macro albuminuric groups are noted to have higher HBA1C levels than the normoalbuminuric group, implying that a tighter glycemic control can reduce the risk of nephropathy.

DISCUSSION

DISCUSSION

The study included 100 diabetic patients without other known comorbids and aged less than 50 years. These patients were subjected to several laboratory investigations namely HBA1C, fasting blood sugar, serum creatinine, serum fibrinogen, serum CRP, urine albumin creatinine ratio and physical findings like BMI, blood pressure were recorded.

Several previous investigators have proposed that diabetes is in itself an inflammatory state and that the grade of diabetic nephropathy corresponds to the severity of the inflammation.

Joydeep Gosh, Mrinal Pal et al showed that serum sialic acid, an inflammatory marker is elevated in diabetics , especially so in diabetic nephropathy cases. The extent of elevation corresponds to the degree of proteinuria. This suggests that diabetes and diabetic nephropathy are inflammatory states.

Sumesh Raj, G.V.Rajan et al showed a similar relationship between the degree of albuminuria and levels of serum ferritin.

Similar studies were conducted with other major acute phase reactants. Vishakha V, Mahajan et al., conducted a study in three major acute phase reactants - serum CRP, serum ceruloplasmin and serum

sialic acid. They demonstrated a positive correlation between the levels of these acute phase reactants and the complications of diabetes especially diabetic nephropathy.

Tan K.C. et al., showed that in diabetes , there is production of advanced end glycation products by non enzymatic reaction which is responsible for a pro-inflammatory state. The inflammation may have a role in the development of the proteinuria.

Michele Dalla Vestra et al showed a significant correlation between the elevated levels of serum fibrinogen, serum CRP, IL 6, SAA and grade of proteinuria. This study revealed that the elevated fibrinogen causes glomerular matrix thickening via inflammatory pathways. This GBM thickening leads to protenuria. This study concluded that low grade inflammation is causes nephropathy by causing basement membrane alterations.

The Casale Monferrato study showed that fibrinogen is a single independent marker to assess the progression diabetic nephropathy.

Chaudhary et al study explained the 3 major mechanisms of progression of albuminuria and its correlation with acute phase reactant. They proposed that elevated levels of acute phase reactants directly injure the glomeruli and thereby alter their function

In our study there is a positive correlation between the levels of CRP- fibrinogen and the severity of albuminuria (measured by urine albumin excretion ratio). This suggests that diabetes itself is a chronic inflammatory state and this inflammatory damage may be responsible for some of the diabetic complications, especially diabetic nephropathy.

Other parameters were also correlated to the grade of albuminuria in the study. Results show that a higher diastolic BP correlates well with a higher degree of albuminuria, but systolic BP did not have a correlation with albuminuria. A study by Azeem Taj et al came up with similar results. It showed that diabetics with a higher blood pressure were more likely to have nephropathy.

Our study also showed that greater BMI levels are associated with higher urinary albumin excretion. Likewise, higher HBA1C levels and greater duration of diabetes were noted to correlate to higher grades of albuminuria. Similar results had been obtained by M.Afkhami et al. However fasting sugar level did not have a significant association with albuminuria in our study.

CONCLUSION

CONCLUSION

Diabetics with a higher blood pressure are more likely to develop nephropathy than the normotensive diabetic people.

A higher body mass index is associated with higher grade of albuminuria. In other words, obese diabetic patients are more prone for developing nephropathy than others.

Higher HBA1C and longer duration of diabetes can lead to more severe nephropathy. Thus a poor glycemic control predicts greater degrees of nephropathy

Acute phase reactants namely serum CRP and serum fibrinogen are elevated in diabetic nephropathy , suggesting that it is an inflammatory state. Hence serum CRP and fibrinogen may be used as predictors of nephropathy in diabetic patients.

LIMITATIONS

LIMITATIONS OF THE STUDY

- The study has included only diabetic nephropathy and has not assessed the other major complications of diabetes.
- Sample size is moderate
- Effects of the anti diabetic medications have not been included in the assessment.

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ANNEXURES

PROFORMA

Name: Age/Sex:

Address: Occupation:

Duration of Diabetes :

i. Blood pressure

ii. Height

iii. Weight

iv. Body mass index

v. Waist hip ratio

Systemic examination

CVS

RS

ABDOMEN

CNS

INVESTIGATIONS

- COMPLETE HEMOGRAM

- URINE ROUTINE :
- URINE ACR :
- SERUM CREATININE :
- 24 HOURS URINE ALBUMIN :
- SERUM CRP :
- SERUM FIBRINOGEN :
- FASTING PLASMA SUGAR :
- ELECTROCARDIOGRAM :
- CHEST X-RAY :
- ULTRASOUND ABDOMEN :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Umaamaheshwari.R.S.
Post Graduate in M.D. General Medicine
Madras Medical College
Chennai 600 003

Dear Dr. Umaamaheshwari.R.S,

The Institutional Ethics Committee has considered your request and approved your study titled **"A STUDY OF CORRELATION BETWEEN LEVELS OF ACUTE PHASE REACTANTS (SERUM CRP, SERUM FIBRINOGEN) AND SEVERITY OF ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS" - NO.07032016.**

The following members of Ethics Committee were present in the meeting hold on **01.03.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD.,Inst.of Pharmacology,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
6.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
7.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3:	Member
8.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
9.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
10.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
11.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

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INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
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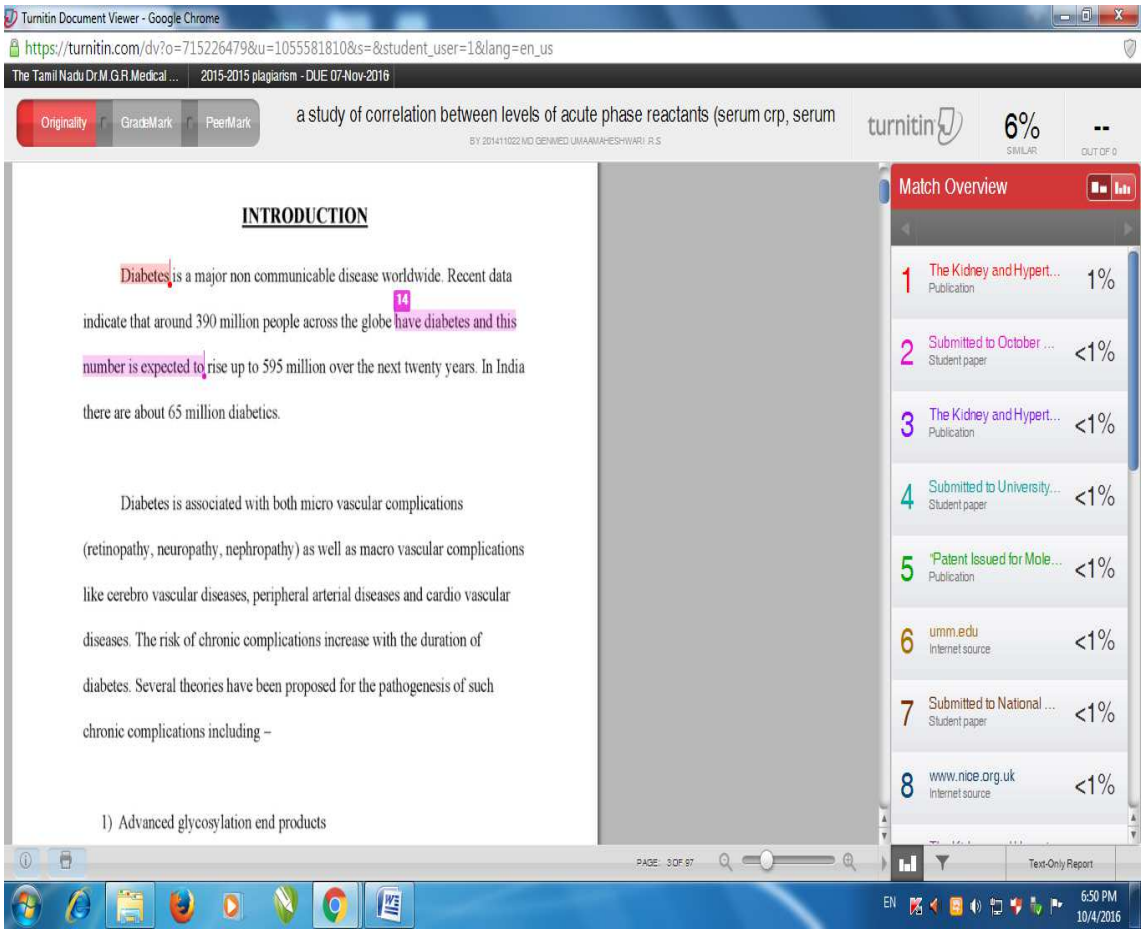
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INTRODUCTION
Diabetes is a major non communicable disease worldwide. Recent data indicate that around 390 million people across the globe have diabetes and this number is expected to rise up to 595 million over the next twenty years. In India there are about 65 million diabetics.
Diabetes is associated with both micro vascular complications (retinopathy, neuropathy, nephropathy) as well as macro vascular complications like cerebro vascular diseases, peripheral arterial diseases and cardio vascular diseases. The risk of chronic complications increase with the duration of diabetes. Several theories have been proposed for the pathogenesis of such chronic complications including –
1) Advanced glycosylation end products
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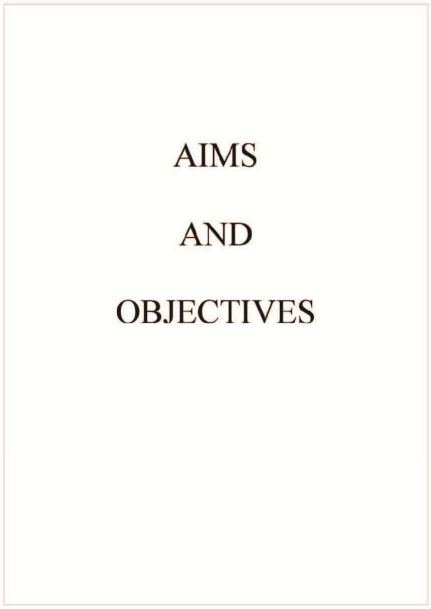

AIMS

AND

OBJECTIVES

INFORMATION SHEET

We are conducting a study - **"A STUDY OF CO-RELATION BETWEEN LEVELS OF ACUTE PHASE REACTANTS (SERUM CRP, SERUM FIBRINOGEN) AND SEVERITY OF ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS "** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to compare the levels of acute phase reactants namely serum CRP and serum Fibrinogen with the levels of albuminuria in patients with type 2 diabetes .

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do certain tests which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Participant Signature of Investigator

Date:

Place:

ஆராய்ச்சி தகவல் தாள்

சென்னை ராஜீவ்காந்தி அரசு பொது மருத்துவமனையின் பொது மருத்துவத்துறையில் "நீரிழிவு நோயாளிகளில் இரத்தத்தில் உள்ள ஃபைப்ரினோஜென் மற்றும் சி-ரியாக்டிவ் புரதம் ஆகியவற்றின் அளவுகளை சிறுநீரின் ஆல்புமின் அளவோடு ஒப்பிட்டு ஆராய்தல்" பற்றிய ஆய்வு நடைபெறுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதனால் தங்களது சிகிச்சையில் பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆய்வில் தங்களுக்கு மருத்துவபரிசோதனை, இரத்தப் பரிசோதனை, ஸ்கேன மற்றும் சிறுநீர் பரிசோதனை செய்யப்படும்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

PATIENT CONSENT FORM

Study Detail : "A STUDY OF CO-RELATION BETWEEN LEVELS OF ACUTE PHASE REACTANTS (SERUM CRP, SERUM FIBRINOGEN) AND SEVERITY OF ALBUMINURIA IN PATIENTS WITH TYPE 2 DIABETES MELLITUS"

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name :
Patient's Age :
Identification Number :

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

e) I hereby consent to participate in this study. ❑

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required. ❑

Signature of Investigator Signature of Participant

Patient's Name and Address

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு

நீரிழிவு நோயாளிகளில் இரத்தத்தில் உள்ள ஃபைப்ரினோஜென் மற்றும் சி-ரியாக்டிவ் புரதம் ஆகியவற்றின் அளவுகளை சிறுநீரின் ஆல்புமின் அளவோடு ஒப்பிட்டு ஆராய்தல்

ஆய்வு நிலையம் : பொது மருத்துவத்துறை,
சென்னை மருத்துவக் கல்லூரி சென்னை - 3.

பங்கு பெறுபவரின் பெயர் :

உள்நோயாளி எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். ☐

இந்த இரு அறுவை சிகிச்சை முறைகளும் ஒப்புக்கொள்ளப்பட்ட முறைகள் என்பதையும் இதனால் உடலுக்கு எந்தவிதமான உபாதைகளும் இருக்காது என்பதை அறிந்துகொண்டு இந்த ஆய்வில் பங்குபெற முழு மனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

இடது கை பெருவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

MASTER CHART

MASTER CHART

S.NO	AGE	SEX	DURATION OF DIABETES	BLOOD PRESSURE		BMI	FBS	HBA1C	CRP	FIBRINOGEN	SR.CREATININE	URINE ACR
				SYSTOLIC	DIASTOLIC							
1	42	M	4	110	80	24.2	140	5.4	4	186	0.4	15
2	36	F	2	124	76	25.1	102	6.1	5	212	0.6	25
3	48	M	10	170	120	32.2	164	9.4	22	412	1.7	1200
4	43	F	3	130	84	23.8	95	5.3	3	342	0.5	100
5	49	F	7	154	86	29.4	230	8.7	26	520	1.9	2100
6	41	M	4	144	80	26.1	122	5.6	2	330	0.9	120
7	43	F	5	120	80	23.4	164	6.4	12	286	1.2	140
8	38	M	2	110	70	22	137	6.1	10	242	1.1	27
9	36	F	2	120	76	24.5	125	5.7	7	295	0.5	110
10	44	M	4	130	80	25	97	7.1	8	204	0.7	29
11	47	M	7	150	96	29.4	176	9.2	32	410	2.1	1400
12	41	M	2	110	70	21.5	149	5.9	6	216	1	15
13	36	F	1	90	70	25.1	153	5.8	5	312	0.6	200
14	45	M	5	164	90	29.5	210	8.7	14	480	2.4	3100
15	38	F	2	114	70	24	122	6.2	4	314	0.5	17
16	43	M	1	120	86	23.1	111	6.1	4	266	1.3	210
17	50	M	4	130	90	32.1	334	7.9	19	574	1.9	1400
18	41	M	2	116	90	22.4	139	7	6	244	0.7	2400
19	44	F	7	150	70	23.4	97	58	7	232	1.1	22
20	46	M	5	160	90	20.8	84	5.9	4	284	1.3	150
21	46	F	2	136	90	34.2	172	8.4	14	514	1.4	3200
22	39	M	1	144	76	22.8	154	7.1	5	194	1.4	140
23	45	F	2	120	80	24.2	178	6.5	6	284	0.7	15
24	47	M	3	110	80	19.9	104	6.4	11	276	1	12
25	49	M	13	146	90	33.7	166	8.3	18	490	1.8	1200
26	43	M	2	120	86	21.7	137	5.8	8	234	0.9	350
27	41	F	1	140	84	20.4	182	7.2	10	174	0.6	20
28	33	M	1	136	90	23.5	110	6.5	7	192	1.2	26
29	40	F	1	144	86	24	94	6.1	12	196	1.1	100
30	39	M	1	110	80	23.2	122	5.7	14	224	0.8	90
31	42	M	2	110	80	35.4	144	7.9	24	484	1.6	1700
32	44	M	3	120	80	22	116	5.4	21	276	1	22
33	50	M	6	160	110	34.7	204	9.7	18	561	1.5	1400

34	48	F	4	130	80	37.8	186	9.9	14	424	1.4	1300
35	49	M	2	120	70	23.7	134	5.9	6	194	1.1	170
36	41	F	1	126	74	24.2	112	6.1	4	196	0.4	11
37	46	M	4	180	100	34.4	148	10.1	21	386	1.9	2100
38	45	M	1	90	76	21	114	6	8	184	0.5	200
39	45	M	1	110	80	22.8	162	5.5	5	214	1	140
40	47	F	2	114	80	21.4	154	5.9	8	236	1.1	19
41	50	M	2	160	110	35.8	156	8.1	24	416	2.1	1100
42	33	F	1	156	70	25.4	122	6.4	8	274	1.3	150
43	42	M	1	120	76	24.2	130	5.9	9	266	0.8	170
44	45	M	1	130	84	21.3	118	7	12	255	0.9	20
45	46	F	1	110	74	26	95	5.5	11	242	1.2	200
46	49	M	4	170	90	34.2	188	7.1	26	434	1.7	24
47	41	M	1	140	90	21	106	5.3	8	184	1.4	140
48	34	M	2	130	86	19.9	104	5.9	10	180	0.9	200
49	50	F	8	144	96	29.8	190	7.7	19	440	3.2	1400
50	43	M	1	110	70	23.2	110	6.4	13	174	0.6	26
51	48	F	5	160	94	28.7	176	8.4	12	210	1.1	1100
52	38	M	2	116	76	21.4	138	6.3	12	210	1.1	100
53	46	F	3	110	70	20.9	140	7.1	11	217	1.2	200
54	41	M	5	130	90	24.1	122	6.4	15	216	0.4	12
55	43	F	4	160	100	22.7	160	5.8	16	284	1.9	130
56	39	F	1	144	70	23	131	5.3	10	266	0.7	19
57	45	F	2	150	76	26	107	6.4	8	255	1.4	28
58	47	M	7	140	96	34.2	146	8.3	14	512	4	2100
59	48	F	4	170	100	22.5	112	7	8	176	1.3	140
60	45	M	2	110	70	25.4	141	6.5	5	184	1.2	200
61	32	F	1	100	80	27.2	148	5.9	4	202	1.5	210
62	39	F	1	128	64	22.9	114	5.4	6	312	0.3	26
63	49	M	5	150	100	33.4	154	7.9	11	490	2.1	1100
64	50	M	4	144	78	21.5	161	5.8	11	244	1.1	24
65	41	M	2	110	70	21	104	6.4	12	262	0.8	16
66	43	M	1	110	76	26	131	6.2	6	232	1.1	140
67	43	F	1	126	84	23.6	98	5.9	6	241	0.9	100
68	42	F	1	130	70	21.4	117	7.1	12	312	1.4	220
69	46	M	4	114	84	22.7	119	6.1	7	296	1.3	400

70	49	F	2	180	116	31	172	10.1	18	424	1.9	2100
71	39	M	2	130	86	23	131	5.4	8	286	0.5	13
72	48	F	1	144	70	24.6	132	7	6	242	0.7	110
73	48	M	1	116	80	21.9	149	6.4	6	322	0.8	240
74	41	F	2	120	78	22	105	5.8	11	142	1	200
75	47	M	5	126	78	21.7	124	6.9	5	345	1.1	160
76	50	M	7	190	120	28.4	166	10.4	24	422	2.4	1700
77	44	M	2	130	84	25.8	91	6.2	10	410	1.4	130
78	36	M	2	124	78	23.6	171	7.8	10	171	1.1	12
79	35	M	1	140	90	21.4	164	7.1	8	280	0.8	200
80	50	F	9	130	96	27.9	170	9	17	450	1.2	1000
81	48	F	2	120	80	22	132	5.4	10	236	1	1100
82	50	M	12	154	90	26	146	9.9	24	412	1.8	900
83	41	F	4	116	74	24.8	122	5.7	4	276	0.5	400
84	43	M	1	130	80	25.1	114	6.2	8	254	1.2	149
85	42	M	2	136	84	22.5	97	5.7	4	302	1.1	28
86	44	M	3	90	76	23.1	158	5.6	6	271	0.7	21
87	50	F	6	160	80	24.1	156	8.7	27	386	1.7	200
88	36	M	1	110	70	20.6	109	6.4	6	259	0.6	140
89	38	F	1	120	74	19.9	127	6	5	231	1	15
90	41	M	2	116	78	26.7	131	5.4	4	208	1.4	240
91	47	F	5	130	80	27.2	162	8.9	19	294	1.5	1100
92	42	M	2	114	80	22.9	114	5.8	10	312	1.1	260
93	49	F	6	140	94	28.4	164	9.1	17	474	3.2	1600
94	41	F	1	140	98	24.5	139	6.3	8	196	1.2	29
95	43	M	1	110	80	23.2	164	7.2	12	289	1.1	220
96	42	M	1	100	76	21.5	109	6.6	4	295	0.6	300
97	50	M	8	166	94	29.7	210	7.7	16	476	1.9	1600
98	39	F	2	110	70	26.1	112	6.4	3	276	0.6	18
99	41	F	2	124	60	24.2	87	5.3	2	402	0.8	400
100	44	F	1	112	70	21.7	86	6.7	11	187	0.9	160

KEY TO MASTER CHART

S.NO	-	SERIAL NUMBER
DM	-	DIABETES MELLITUS
FBS	-	FASTING BLOOD SUGAR
HBA1C	-	GLYCOSYLATED HEMOGLOBIN
CRP	-	C-REACTIVE PROTEIN
ACR	-	ALBUMIN CREATINIE RATIO
BMI	-	BODY MASS INDEX